

Enzyme Essential for Muscle Nourishment is Inactive in Children with Duchenne Muscular Dystrophy

Background: Exercise is good for most people: it helps to preserve strength, improve general function, and regulate energy expenditure. Paradoxically, children with Duchenne Muscular Dystrophy (DMD) do not benefit from exercise; clinical observations suggest they may fare worse after engaging in exercise programs. The physiological basis of this problem is not well understood. However, researchers have established that muscle contractions in DMD are impaired because a muscle protein, dystrophin, is either missing or defective.

Advance: In healthy people, muscle contractions set off a sequence of events resulting in release of nitric oxide, a blood vessel-dilating substance. Researchers discovered that muscle contractions in DMD patients do not stimulate a compensatory increase in blood flow because nitric oxide synthase, an enzyme that produces nitric oxide, does not attach to the defective dystrophin protein. Consequently, nitric oxide is not produced, blood flow does not increase, and the muscles do not receive adequate nourishment.

Implications: Therapeutic approaches to facilitate nitric oxide production in the absence of functioning dystrophin might be devised to allow more blood to enter the muscles of DMD children during exercise. Being able to tolerate even a slightly higher level of exercise might allow DMD children to achieve a higher level of physical functioning through enhanced use of their weakened muscles. Any preservation of existing function, or minimization of the rate of functional loss, would be of immense value in slowing the progression of this disabling and, eventually, fatal disease.

Sander M, Chavoshan B, Harris SA, Iannaccone ST, Stull JT, Thomas GD, and Victor RG: Functional muscle ischemia in neuronal nitric oxide synthase-deficient skeletal muscle of children with Duchenne muscular dystrophy. Proceedings of the National Academy of Sciences USA 97: 13818-12823, 2000.

Reduced Fat Intake to Lower Cholesterol is Safe and Beneficial for Children

Background: Because atherosclerosis begins in childhood, low-fat, low-cholesterol diets are recommended for healthy children 2 years of age and older, particularly those who have elevated blood cholesterol and a family history of premature coronary heart disease (CHD). However, questions have been raised about the safety of diets reduced in total fat and the ability of diets reduced in saturated fat and cholesterol to improve blood lipid levels in children.

Advance: The Dietary Intervention Study in Children (DISC) showed that children with high blood cholesterol levels can benefit from reducing the amounts of fat and cholesterol in their diets without adversely affecting their development. A low-fat, low-cholesterol diet does not affect the growth, nutritional status, or sexual maturation of children. Furthermore, the diet helps them decrease their low-density lipoprotein, or "bad" cholesterol, levels.

Implications: The results allayed concerns that diets reduced in fat and cholesterol could have adverse effects on growth and nutritional status. A heart-healthy diet that can reduce LDL-cholesterol levels during childhood and adolescence is expected to reduce future risk for CHD, particularly in light of evidence that healthy eating patterns and other positive habits established early in life may carry forward into adulthood.

Obarzanek E, Kimm SYS, Barton BA, Van Horn L, Kwiterovich PO, Simons-Morton DG, Hunsberger SA, Lasser NL, Robson AM, Franklin FA, Lauer RM, Stevens VJ, Friedman LA, Dorgan JF, and Greenlick MR: Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: seven-year results of the Dietary Intervention Study in Children (DISC). Pediatrics 107: 256-264, 2001.

When it Comes to Exercise, Every Little Bit Helps To Prevent Coronary Heart Disease

Background: Coronary heart disease (CHD) is the leading cause of death among women in the U. S. Although physical inactivity is a well-established risk factor for CHD, it was unclear how often a woman needs to exercise in order to reduce her risk and what the duration and intensity of each exercise session should be. Also, very little was known about the extent to which exercise benefits women who are at higher-than-normal risk for CHD (e.g., smokers, obese women).

Advance: Researchers found that participating in mild-to-moderate levels of physical activity decreases a woman's risk of CHD. Walking at least one hour per week at a pace of 2 miles per hour was beneficial compared with no regular walking. Moreover, the authors found that time spent walking was more predictive of lower CHD risk than walking pace. These results apply not only to women with average risk for CHD, but also to those who are at high risk because of smoking, overweight, or high cholesterol levels.

Implications: The findings indicate that even one hour of walking per week – an activity within the ability of most women – can reduce CHD risk.

Lee IM, Rexrode KM, Cook NR, Manson JE, and Buring JE: Physical activity and coronary heart disease in women – is "no pain, no gain" passé? The Journal of the American Medical Association 285: 1447-1454, 2001.

Counseling Helps Women, But Not Men, Improve Fitness

Background: Physical inactivity is an important risk factor for many prevalent diseases and conditions, including coronary heart disease, hypertension, diabetes, and obesity. National data indicate that only about 20 percent of U.S. adults report participating in regular, sustained physical activity for 30 minutes five or more days a week, which is the current recommendation to improve health and prevent disease.

The Activity Counseling Trial (ACT) tested the effects of two physical activity counseling programs conducted in primary medical care settings for sedentary patients. The programs were compared with the currently recommended intervention of physician advice and educational materials. One program consisted of counseling sessions at the time of physician visits plus interactive mail such as monthly newsletters and mailed feedback. The second program comprised the same components plus regular telephone counseling and behavioral classes.

Advance: The cardiorespiratory fitness of the women in both counseling programs significantly increased over a 2-year period. Although the two programs varied in intensity (an average of 22 contacts for a total of 3 hours versus an average of 44 contacts totaling 9 hours over two years), they were equally effective.

Despite a statistically significant increase in self-reported physical activity associated with all three interventions for either sex, no improvement in fitness levels was observed after 24 months for any of the men's groups or for the women who received physician advice only. All three men's interventions were associated with a significant increase in fitness six months after the study began, but the improvements were not sustained and all groups of men reverted to the initial fitness level by the end of the study.

Implications: The ACT counseling interventions were successful in improving the cardiorespiratory fitness of women, but not of men. Therefore, it would seem advisable to use these, or similar, interventions only for inactive women patients interested in increasing their physical activity.

The Writing Group for the Activity Counseling Trial Research Group: Effects of physical activity counseling in primary care: the Activity Counseling Trial: a randomized controlled trial. The Journal of the American Medical Association 286: 677-687, 2001

Mediator of Transfusion-Induced Fever is Identified

Background: Millions of blood platelet transfusions are performed each year, and febrile reactions occur in 30 percent or more of them. Most of the reactions are mild, but occasionally, patients experience acute lung injury and life-threatening pulmonary failure. Proteins known as cytokines, which are responsible for intercellular communication, have been associated with occurrence of febrile reactions. Some of them have been found in stored platelet preparations, but the mechanisms by which they or other specific mediators might induce fever after platelet transfusion have not been identified.

Advance: Investigators recently reported that a previously identified signaling molecule called CD154 is released from platelets during their collection, processing, and storage. CD154 is able to stimulate production of several proinflammatory cytokines and factors associated with fever induction, such as prostaglandin E₂ and cyclo-oxygenase-2.

Implications: Identification of CD154 as a prime candidate in causing transfusion-associated fever may lead to methods to block its release during platelet preparation or to remove it before transfusion, thereby preventing adverse reactions. Screening potential platelet donors could also be done routinely to rule out those with abnormally high levels of CD154.

Phipps RP, Kaufman J, and Blumberg N: Platelet derived CD154 (CD40 ligand) and febrile responses to transfusion. The Lancet 357: 2023-2024, 2001.

Symptomatic Congenital Cytomegalovirus Infection in Infants of Women with Preconceptional Immunity

Background: Congenital cytomegalovirus (CMV) infection is among the leading causes of brain damage and sensorineural hearing loss in children in the U.S. NIH-supported investigators continue to study the significant contribution of CMV infection to infant morbidity, which includes progressive onset of hearing impairment during early childhood.

Advance: A recent study shows that women with preconceptional immunity to one strain of CMV can transmit a different CMV strain to their developing babies causing symptomatic congenital infection. This result is crucial for understanding the components of protective immunity and for developing effective vaccines against congenital CMV infections. These findings suggest that a vaccine against only one strain of CMV is unlikely to provide adequate protection against CMV reinfection in pregnant women.

Implications: This work will guide the development of public health approaches (e.g., neonatal CMV screening, vaccine development, drug development, etc.) that will be effective in reducing and eventually eliminating this highly significant congenital health problem.

Boppana SB, Rivera LB, Fowler KB, Mach M, and Britt WJ: Intrauterine transmission of cytomegalovirus to infants of women with preconceptional immunity. The New England Journal of Medicine 344: 1366-1371, 2001.

Effects of Socioeconomic Status on Aphasia Severity and Recovery

Background: Low levels of educational attainment and low occupational status have been found to be associated with poor health, increased incidence of disease and shorter life span. However, the specific correlation of these two socioeconomic factors with both initial severity of aphasia (the language problems associated with stroke or other types of brain damage) and subsequent recovery from aphasia has not been examined. Educational level and literacy have been explored in relation to aphasia severity, with varied and often conflicting conclusions.

Advance: NIH investigators examined the histories of a group of persons with aphasia due to a single, unilateral left-hemisphere lesion, at two points in time: at approximately four months post-onset, and at 8-9 years post onset. Severity of aphasia at these two points in time was determined using the Boston Diagnostic Aphasia Examination. Education and occupation correlated significantly with aphasia severity. The lower the level of educational attainment and occupational status, the more severe was the aphasia, both at 4 months as well as at 8-9 years post-onset. However, the rate of recovery was the same, regardless of level of education or occupation. Lesion size did not explain the differences in the severity ratings for the high and low education and occupation groups.

The influence of education and occupation on aphasia in the early stages is consistent with reports from other studies demonstrating links between socioeconomic status (SES) and severity of illness in many organ systems. What is more difficult to explain is the lack of influence of educational or occupational level on rate of recovery.

Implications: These results address the need for ensuring access to care and rehabilitation, since the potential for recovery exists for individuals regardless of education and occupation.

Connor LT, Obler LK, Tocco M, Fitzpatrick PM, and Albert ML: Effect of socioeconomic status on aphasia severity and recovery. Brain and Language 78: 254-257, 2001.

Spoken and Written Language Disabilities in School-Aged Children

Background: Many previous investigations of young children with language impairments have focused on errors of grammatical morphology in spoken language. However, much less is known about the persistence of these grammatical errors or about the occurrence of errors in written language.

Advance: NIH-supported researchers examined the spoken and written abilities of a group of sixty school-aged children. Areas examined included use of morphemes that mark verb finiteness (regular past tense, third person singular present tense, and forms of the verb “to be”), as well as noun morphology (such as regular plural, possessive, and articles). Children with normal language skills had mastered the verb and noun morphology in spoken and written language. Children with language learning disabilities showed substantial difficulty in the written samples. These results indicate that particular aspects of the written grammar remain an area of relative difficulty for children with language learning difficulties. Due to the visibility and permanence of written language, the consequences of grammatical errors that persist in writing in the upper elementary school years and beyond should not be underestimated. Researchers found that these errors cluster in a limited number of types, increasing the chance that intervention can be targeted and effective.

Implications: The results of this study emphasize the need to evaluate children’s written language skills.

Windsor J, Scott CM, and Street CK: Verb and noun morphology in the spoken and written language of children with language learning disabilities. Journal of Speech, Language, and Hearing Research 43: 1322-1336, 2000.

Phase I Clinical Trial of an Otitis Media Vaccine Candidate

Background: Otitis media is the most common reason for a sick child to be evaluated by a physician, a public health burden estimated to be five billion dollars a year. In addition to the cost implication, prevention of otitis media is particularly important because repeated antibiotic treatment of otitis media often results in the appearance of drug-resistant strains of bacteria.

Advance: NIH scientists have developed candidate vaccines that would protect infants from otitis media caused by two major bacterial pathogens: nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis*. These two pathogens account for two thirds of otitis media cases in children, and there is no vaccine available for prevention of the disease. The scientists used a bacterial surface antigen, lipooligosaccharide, as a vaccine component to make conjugate vaccines. Pre-clinical testing with such vaccines from nontypeable *H. influenzae* demonstrated that parenteral or mucosal administration with the vaccines could generate specific immunity against the bacteria and reduce bacterial colonization in nasopharynx or reduce the incidence of experimental otitis media in animal models. In a Phase I clinical trial involving forty normal human adult volunteers, one such vaccine proved to be both safe and effective, eliciting a significant immune response against the bacteria. This candidate vaccine will soon be tested in a second trial for safety and effectiveness in the pediatric population. For *Moraxella catarrhalis*, similar approaches were taken, resulting in several candidate vaccines. Pre-clinical testing in animal models with vaccines for *Moraxella catarrhalis* demonstrated that the vaccines were safe and effective, eliciting a significant immune response against the bacterial colonization.

Implications: Current and future studies for *Moraxella catarrhalis* include development of two new serotype conjugate vaccines, followed by Phase 1 clinical trials to test these candidate vaccines for safety and efficacy in humans. These studies are significant advances towards the long-term goal of developing a multivalent vaccine that prevents otitis media in children.

Hu WG, Chen J, Battey JF, and Gu XX: Enhancement of clearance of bacterial from murine lungs by immunization with detoxified lipooligosaccharide from *Moraxella catarrhalis* conjugated to proteins. Infection and Immunity 68: 4980-4985, 2000.

Hu WG, Chen J, McMichael JC, and Gu XX: Functional characteristics of a protective monoclonal antibody against serotype A and C lipooligosaccharides from *Moraxella catarrhalis*. Infection and Immunity 69: 1358-1363, 2001.

Physical Exercise Prevents Disability in Older Persons with Arthritis

Background: Older persons with osteoarthritis of the knee often have difficulty doing basic activities of daily living (ADLs), including walking, eating, dressing, using the toilet, bathing, or even moving from bed to a chair. These ADL disabilities are extremely important because they severely limit independence and strongly predict the necessity for institutionalized long-term care. Whether older persons with osteoarthritis of the knee should increase or decrease their activity level to maintain mobility and prevent disability is controversial. Although previous exercise interventions have shown positive effects, none has yet been shown to affect clinically significant outcomes such as ADLs.

Advance: Researchers recently conducted a study of exercise in 250 community-dwelling persons, 60 years of age or older, with knee osteoarthritis. These individuals were initially able to perform the ADLs, but were likely to develop progressive disability due to advancing osteoarthritis. The participants were divided into three groups. Two groups participated in exercise programs: an aerobic exercise program to increase endurance, or a resistance training program to increase strength. The third group did not participate in structured exercise programs and served as a control group. ADL disability was measured every three months throughout the eighteen months of the study. Participants in both exercise programs had lower incidences of ADL disability than those in the control group. The strength training program reduced the risk for ADL disability by 40 percent; and the aerobic exercise program reduced the risk by 47 percent. Individuals who complied most diligently with the exercise program had the lowest risk for disability.

Implications: This study demonstrates that exercise, either designed to increase endurance or to increase strength can help older people with osteoarthritis of the knee retain the ability to perform activities of daily living. It suggests that creating such exercise programs has great potential to prolong the independence of older persons despite the presence of this common, and often disabling, disease.

Penninx BWJH, Messier SP, Rejeski WJ, Williamson JD, DiBari M, Cavazzini C, Applegate WB, and Pahor M: Physical exercise and prevention of ADL disability in older persons with osteoarthritis. Archives of Internal Medicine (in press 2001).

Reducing Delirium after Hip Fracture in Older Adults

Background: Delirium is an acute confusional state that complicates recovery from hip fracture repair in at least one-third of the 250,000 older Americans who fracture a hip each year. Besides being frightening to patients and their families, and difficult to manage in the hospital, delirium after hip fracture is also associated with poor functional recovery.

Advance: In a recent study aimed at reducing risk factors for delirium, geriatricians provided a variety of recommendations to the orthopedic physicians caring for the hip-fracture patients. These recommendations included blood transfusion to maintain an adequate red blood cell count, limiting the use of psychoactive medications and removing urinary catheters by the second day after surgery. Other recommendations related to pain management, nutrition, drug interactions and prevention, and detection and treatment of postoperative complications. This intervention led to a one-third reduction in patients who subsequently developed delirium and a one-half reduction in the proportion who subsequently developed severe delirium compared to a control group of patients who did not receive the intervention.

Implications: This study successfully demonstrates that measures can be taken to prevent delirium in vulnerable older patients. These measures offer great promise for improved treatment of these patients. Reducing the episodes of acute confusion that are frightening to patients and limit their ability to participate adequately in their medical care during hospitalization is an important accomplishment. The successful prevention of delirium described here was performed in a single medical center by a small group of health providers. This approach needs to be studied more widely with diverse groups of patients and medical personnel to document whether it should be adopted as a routine part of hospital treatment for older persons recovering from hip fracture surgery.

Marcantonio ER, Flacker JM, Wright J, and Resnick NM: Reducing delirium after hip fracture: a randomized trial, Journal of the American Geriatrics Society 49: 516-522, 2001.

Marcantonio ER, Flacker JM, Michaels M, and Resnick NM: Delirium is independently associated with poor functional recovery after hip fracture. Journal of the American Geriatrics Society 48: 618-624, 2000.

Psychological Benefits of Exercise in the Elderly

Background: Increasing evidence suggests that regular physical activity can have considerable psychological as well as physical benefits in the elderly, such as increasing one's sense of well-being. However, little is known about the factors that underlie any such change brought about by exercise. Although factors such as the amount of exercise may be implicated in exercise-induced improvements in sense of well being, it has also been suggested that social factors might influence this relationship. However, to date, the contribution of the social environment while exercising has been unclear.

Advance: This study examined whether different exercise settings influence emotional responses (positive well being, psychological distress, and feelings of fatigue) independent of the effects of exercise intensity and duration in older adults (average age of 66 years). Also examined were changes in exercise self-efficacy, that is, the belief in being physically capable of successfully completing a given exercise routine. Exercising in a social environment resulted in greater improvements in positive well-being and reductions in psychological distress than when the participants exercised alone, controlling for the level and duration of the exercise. In addition, older adults who showed greater increases in self-efficacy also demonstrated more pronounced affective improvement with activity, primarily in the group/social exercise conditions. These findings suggest that psychosocial responses to exercise are not determined exclusively by physiological factors. Rather, the environmental context in which one exercises is partially responsible for the increased well-being.

Implications: As the aging population increases in the U.S., improving the quality of life will be a priority for older Americans. Since this study offers evidence supporting the importance of social environment on physical and mental health outcomes of an intervention like exercise, this research has major implications regarding the potential benefits of group environment and social support on well-being. Social engagement appears to have direct positive health implications for older individuals.

McAuley E, Blissmer B, Katula J, and Duncan TE: Exercise environment, self-efficacy, and affective responses to acute exercise in older adults. Psychology and Health 15: 341-355, 2000.

Women Caring for Family Members with Dementia Can Benefit from an Exercise Program

Background: It is now recognized that caregiving burdens can result in a variety of negative health outcomes. Researchers have shown that individuals who exercise can benefit in terms of lower stress-induced high blood pressure and improvement in self-reported quality of sleep. Yet, no previous studies have specifically examined the impact of sustained physical activity on older caregivers. This study is the first to examine the role that a regular moderate-intensity exercise program plays in the enhancement of health and quality of life for women caring for loved ones with dementia.

Advance: This study explores the use of an in-home, telephone-based counseling program delivered by a trained health educator. This one-year study involved a sample of 100 women age 49 to 82 years who were sedentary, free of cardiovascular disease, and caring for a relative with dementia. Participants received either a home-based, telephone-supervised moderate-intensity exercise training or nutrition education program. Exercise consisted of brisk walking for four 30- to 40-minute sessions per week. Compared with the nutrition education group, exercise participants showed clinically significant improvements in physical activity levels, stress-induced blood pressure reactions, and sleep quality. The nutrition group reported significant improvements in percentages of total calories from fats and saturated fats relative to exercisers. Significant reductions were also observed among nutrition participants in daily servings of fats, oils, sweets, and high-fat snacks. Both groups reported significant improvements in psychological distress, including depressive symptoms and self-rated stress.

Implications: Understanding how best to tailor programs to the needs and preferences of different populations remains a critical public health challenge. This research demonstrates that properly tailored health promotion programs can improve the health and functioning of older women family caregivers.

King AC, Baumann K, O'Sullivan P, Wilcox S, and Castro C: Effects of moderate-intensity exercise on physiological, behavioral, and emotional responses to family caregiving: A randomized controlled trial. Journal of Gerontology: Medical Sciences (in press 2001).

Estrogen May Attenuate the Age-Associated Systolic Blood Pressure Rise in Post-Menopausal Women

Background: Although systolic blood pressure (SBP) is generally higher in men than women until middle age, this gender difference disappears after the menopause, due to an accelerated rise in SBP in older women. Although the reason for this accelerated rise in SBP is unclear, the loss of endogenous estrogen production that accompanies menopause may be responsible.

Advance: Both cross-sectional and longitudinal data from the Baltimore Longitudinal Study of Aging (BLSA) suggest that estrogen replacement therapy (ERT) in healthy post-menopausal women attenuates their age-associated increase in systolic blood pressure. In the first study, 77 postmenopausal BLSA women aged 67 ± 11 years who were receiving ERT had lower SBP, as well as lower diastolic BP when compared to 57 women of similar age who were not receiving ERT.

To confirm these cross-sectional findings, investigators compared longitudinal blood pressure changes in 77 BLSA women who remained on ERT for a mean of 5.2 years to those of 149 similar women who did not take estrogen. Although baseline characteristics such as age, education, physical activity habits, body fatness, smoking status, and cholesterol levels were similar in the two groups, the rise in SBP was less pronounced in the women receiving ERT. Furthermore, this beneficial effect of ERT was more prominent in women who began ERT at older ages, and in more obese women. Statistical analyses showed that the rise in SBP per decade in a 55-year old woman on ERT was 7.6 mm Hg compared to 18.7 mm Hg in a non-user. Diastolic BP, however, did not change significantly over time in either group.

Implications: These studies suggest that ERT may attenuate the brisk rise in SBP that occurs with age in healthy postmenopausal women. Because the age-associated rise in SBP is an important risk factor for future coronary events and stroke, these data further suggest that long-term ERT may reduce cardiovascular risk in this large subset of the population. Definitive determination of whether estrogen exerts a protective effect will require analysis of clinical trials such as the ongoing Women's Health and Aging Study.

Scuteri A, Lakatta EG, Bos AJG, and Fleg JL: Effect of estrogen and progestin replacement on arterial stiffness indices in postmenopausal women. Aging 13: 122-130, 2001.

Scuteri A, Bos AJG, Brant LJ, Talbot L, Lakatta EG, and Fleg JL: Hormone replacement therapy and longitudinal changes in blood pressure in postmenopausal women. Annals of Intern Medicine 135: 229-238, 2001.

Dietary Restriction Increases Levels of Growth Factors in the Brain and Stimulates Production of New Nerve Cells

Background: Reducing calorie intake can increase the lifespan of rodents. Recent findings suggest that such dietary restriction (DR) can also promote survival of brain cells in rodents exposed to insults like those occurring in several neurodegenerative disorders. The cellular and molecular mechanisms responsible for the beneficial effects of DR on the brain are unknown. Brain function might be preserved after an insult or during aging in a number of ways, including the production of neuronal growth factors that support the survival and growth of neurons, and the production of new neurons produced from so-called “stem” cells that are present in the adult brain. In studies of mice and rats, investigators have discovered that DR can affect both the production of growth factors and new neurons in the brain.

Advance: Adult rats and mice were maintained on a DR feeding regimen (every other day feeding), or were fed ad libitum (on demand), for 3 months. Levels of the neuronal growth factor, brain-derived neurotrophic factor (BDNF), were significantly increased in the hippocampus, a brain region involved in learning and memory, as well as in several other brain regions of rats maintained on the DR regimen compared to animals fed ad libitum. Seizure-induced damage to neurons in the hippocampus was significantly reduced in animals maintained on DR. When an antibody that blocks BDNF activity was introduced into the brain, the beneficial effect of DR was decreased, showing that increased levels of BDNF were responsible for protection. When rats were maintained on a DR feeding regimen, they also exhibited a significant increase in the numbers of newly divided cells in a region of the hippocampus called the dentate gyrus. Additional analyses showed that many of these new cells became neurons.

Implications: These findings provide the first evidence that diet can affect expression of a neurotrophic factor and can also stimulate the production of new neurons in the brain. These findings may help to explain the beneficial effects of DR on learning and memory in animals. They also may have implications for developing new ways to combat age-related neurodegenerative disorders.

Duan W, Guo Z, and Mattson MP: Brain-derived neurotrophic factor mediates an excitoprotective effect of dietary restriction in mice. Journal of Neurochemistry. 76: 619-626, 2001.

Lee J, Duan W, Long JM, Ingram DK, and Mattson MP: Dietary restriction increases the number of newly generated neural cells, and induces BDNF expression, in the dentate gyrus of rats. Journal of Molecular Neuroscience. 15: 99-108, 2000.

Vaccination with Amyloid-beta Peptides Prevents Age-related Memory Deficits in a Transgenic Animal Model of Alzheimer's Disease

Background: One defining characteristic of Alzheimer's disease (AD) is the accumulation of amyloid plaques that are formed in the brain from amyloid-beta (A_β), a peptide fragment of amyloid precursor protein (APP). In 1999, researchers showed that long-term vaccination with A_β peptides caused reductions in the deposition of amyloid in APP transgenic mice. This finding suggested that vaccination against amyloid deposition might be of benefit in humans, but whether a reduction in amyloid would also mean an improvement in learning and memory had not been studied. Also, it had not been determined if the vaccination procedure could have any adverse effects. For example, it was possible that inflammation caused by vaccination might interfere with normal brain function or cause degenerative changes in the brain. To answer these questions, a vaccination study was conducted using both the APP transgenic mouse model and a second transgenic mouse that over-expressed both mutant APP and Presenilin 1 (PS1). PS1 is a protein made by the PS1 gene whose mutations are responsible for the majority of inherited early-onset AD. These transgenic mice develop amyloid deposits as they age that are very similar to those seen in AD in humans.

Advance: Transgenic mice were inoculated with A_β in either a long-term study (over nine months) or in a short-term study (over two months) and tested for memory deficits in a maze. Untreated control mice have increases in amyloid as they age that are associated with diminished memory performance. Mice vaccinated in the long-term study had a partial reduction in amyloid deposition, and were dramatically superior in memory performance compared to control transgenic mice immunized with an irrelevant protein. Mice vaccinated over the short-term had no detectable change in amyloid pathology, but demonstrated an increase in microglial activation. Remarkably, mice vaccinated over the short term also performed better on learning and memory tasks. The benefit of the vaccination was found in both kinds of transgenic mice tested. Any inflammatory responses that may have been caused by the vaccine did not adversely affect performance in this learning and memory task.

Implications: These findings indicate that vaccination with A_β peptide protects transgenic mice from the age-related learning and memory deficits that occur in this mouse model for AD. Although the mechanism by which immunization with A_β blocks learning and memory deficits is not understood and it is too early to know whether these findings in mice will also be valid in humans, these findings strongly support further exploration of this therapeutic approach to the prevention and possible treatment of AD.

Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C, Hardy J, Duff K, Jantzen P, DiCarlo G, Wilcock D, Connor K, Hatcher J, Hope C, Gordon M, and Arendash GW: A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. Nature 408: 982-985, 2000.

Environment May Protect Against Cognitive Decline and Alzheimer's Disease (AD)

Background: High levels of education and occupation are correlated with protection against cognitive decline and the development of AD. One mechanism for this protection might be through mental stimulation, perhaps by increasing brain activity and maximizing the number of active brain cells and the connections between them. Similarly, lack of close social ties has been correlated with increased risk for mortality and possibly also for cognitive decline and dementia. Two recent studies have explored the links between environmental factors and cognitive decline.

Advance: Investigators in the first study reasoned that recreational activities might be an excellent measure of mental activity as they are less strongly influenced by economic and social factors than the number of years of formal education. They recorded the extent to which 500 AD patients and age-matched healthy controls had participated in recreational activities classified as passive (e.g., watching television), intellectual (e.g., chess, crossword puzzles), or physical (e.g., bowling, skating) over their adult life. Patients with AD were found to have been much less active than healthy control persons of similar background in terms of both diversity and intensity of recreational activities engaged in during early and middle adulthood. These differences were not explained by differing educational or income levels, age, or gender. People relatively inactive in midlife had a two and a half fold increased risk of developing AD. Differences were greatest for intellectual activities, but were significant for passive and physical activities as well. In a separate study, the relationship of social ties and support to patterns of cognitive aging over a 7.5 year period was examined in 1200 high functioning, community-dwelling older adults aged 70-79, who were enrolled in the MacArthur Successful Aging Study. The results showed that greater baseline emotional support was a significant predictor of better cognitive function at the 7.5-year follow-up, controlling for baseline cognitive function and known socio-demographic, behavioral, psychological, and health status predictors of cognitive aging.

Implications: These findings demonstrate the importance of further assessing the possible role of physical, intellectual, and social stimulation in protecting against cognitive decline in the elderly. Such findings are provocative and may have important significance for public policy. One should caution, however, that the disease may develop several decades before symptom onset and very early deficits might be the cause rather than the effect of lowered participation in recreational activities and/or social relationships.

Friedland, RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Hsiun Chen CH, Petot GJ, and Debanne SM: Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. Proceedings of the National Academy of Sciences USA 98: 3440-3445, 2001.

Seeman TE, Lusignolo TM, Albert M, and Berkman L: Social relationships, social support and patterns of cognitive aging in healthy, high functioning older adults: MacArthur studies of successful aging. Health Psychology (in press 2001).

Statins May Reduce the Risk of Alzheimer's Disease

Background: There is increasing evidence suggesting that high levels of cholesterol may have a role in the development of Alzheimer's disease (AD). For example, APOE4, a gene involved in lipid metabolism, is a risk factor for AD. In addition, epidemiological studies have linked risk factors for vascular disease to dementia. Basic laboratory studies have shown that cholesterol can increase production of the amyloid peptide, the substance that forms plaques in the brains of AD patients. The precise mechanisms by which these factors might be associated with dementia are poorly understood at present. Two epidemiology studies explored the possibility that the use of statins, the most common form of cholesterol-lowering drugs, might lower the risk of developing AD. The first study involved over 1300 persons in a United Kingdom research database and the second involved over 56,000 persons in 3 hospital databases in the U.S. A third study investigated the effect of a high fat/cholesterol diet on brain pathology in a mouse model of AD.

Advance: The first study showed that individuals who were prescribed statins had a risk of dementia 70 percent lower than those who did not have high cholesterol or who were not on lipid lowering treatment. The effect was similar regardless of the type of statin prescribed. People with high cholesterol prescribed a non-statin drug or those who remained untreated did not have reduced risk for dementia, showing that the effect was not due to lowering lipid levels per se. The second study showed a similar relationship between both lovastatin or pravastatin prescription and a 60-73 percent lowered risk of developing AD. This relationship was not found with other medications for hypertension or cardiovascular disease. The third study used a transgenic mouse model of AD in which amyloid plaques accumulate in the brain with age. Mice fed a high cholesterol diet were compared to mice on a normal diet. After seven weeks, the mice fed the high cholesterol diet had much higher levels of blood cholesterol and the mean number of amyloid deposits in their brains was 65 percent higher than those on the normal diet.

Implications: These findings suggest that the use of statins to lower blood cholesterol levels could substantially reduce the risk for dementia in older individuals. Further research is needed to confirm these findings and explore the molecular mechanisms by which statins reduce the risk of AD.

Jick H, Zornberg GL, Jick SS, Seshadri S, and Drachman DA: Statins and the risk of dementia. Lancet 356: 1627-1631, 2000.

Wolozin B, Kellman W, Ruosseau P, Celesia GG, and Siegel G: Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Archives of Neurology 57: 1439-1443, 2000.

Refolo LM, Pappola MA, Malester B, LaFrancois J, Bryant-Thomas T, Wang, R, Tint GS, Sambamurti K and Duff K: Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiology. Disease 7: 321-333, 2000.

Small Particles in Air May Trigger Heart Attacks

Background: NIH has supported much of the research on the health effects of small particulate matter found in air pollution. This research has linked exposure to particulate matter with increased risk of cardiovascular diseases. Fine particles are produced by combustion processes in car engines, power plants, refineries, smelters, and other industries. Small particles can penetrate deeply into the air exchange regions of the lung bypassing the normal defense mechanisms of the lung. The current study is the first to link short-term transient effects of particulate matter less than 2.5 microns (PM_{2.5}) in size to the risk of heart attack.

Advance: Regional air pollution measurements taken at the time study participants in the Boston area said their heart attack symptoms began were compared to measurements taken during control periods. The risk of heart attack was about 1.5 times higher among those exposed to elevated PM_{2.5} in the two hours prior to the development of symptoms. The risk was even greater (about 1.7 times higher) when PM_{2.5} levels were increased for 24 hours prior to symptoms. The PM_{2.5} levels were high, but at levels that occur frequently in many parts of the U.S. Other recent data suggest that exposure to high PM_{2.5} levels may cause increased systemic inflammation, increased blood thickness, and an increase in C-reactive protein which causes the formation of blood clots.

Implications: This study provides strong evidence that short-term exposure to PM_{2.5} causes increased risk of heart attack. Knowing the time between exposure and heart attack is crucial to determining the biological mechanisms responsible for the associations. This study is also very important in establishing proper regulatory standards for PM_{2.5} to reduce the risk for the population, especially susceptible sub-populations.

Peters A, Dockery DW, Muller JE, and Mittleman MA: Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103: 2810-2815, 2001.

Women's Cancer Risk Linked with Nitrate Levels in Drinking Water

Background: Nitrate contamination of drinking water has been documented in many areas of the U.S.. The source of the nitrate has been attributed to widespread use of commercial fertilizers as well as animal and human wastes. In Iowa, the use of fertilizers in both rural and urban settings has resulted in 30 percent to 40 percent of the public water supply with nitrate concentrations greater than 5 mg/liter. The Environmental Protection Agency (EPA) limit for nitrate in drinking water is 10mg/liter primarily to prevent methemoglobinemia (an inability of blood to carry oxygen) in infants. However, other health risks of nitrate exposure have not been fully evaluated against this standard.

These investigators were interested in evaluating nitrate consumption and cancer risk. Nitrates are converted to highly carcinogenic N-nitroso compounds in the digestive track. An epidemiologic study was conducted using the Iowa Women's Health Study cohort. Drinking water source is but one of the many issues this study tracks and with over 40,000 women enrolled, it is an excellent resource for this type of investigation.

Advance: As in previous studies, these investigators found a positive association between nitrate exposure and bladder cancer. Unexpectedly, they also found a positive association for ovarian cancer. In addition, they reported a negative association for uterine and rectal cancer. All associations appear to be dose dependent. There were no associations for all other cancer types examined.

Implications: Results from these studies correlate with earlier studies that show increased risk for bladder cancer as nitrate level in drinking water rises. The unexpected positive association with ovarian cancer and the even more unexpected negative associations for uterine and rectal cancer suggest that nitrate levels below the current EPA standard in municipal water supplies are of significant public health concern. Additional research is necessary to fully understand this issue and to make standards to protect public health.

Weyer PJ, Cerhan JR, Kross BC, Hallberg GR, Kantamneni J, Breuer G, Jones MP, Zheng W, and Lynch CF: Municipal drinking water nitrate level and cancer risk in older women: the Iowa women's health study. Epidemiology 11: 327-338, 2001.

The DDT Metabolite Associated with Increased Risk of Premature Birth

Background: DDT (1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane) was banned or restricted in industrialized countries in the 1970s, but it is still widely used against malaria-transmitting mosquitoes in many countries. Although no longer used in this country, it degrades into a highly persistent compound, DDE (1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene) and exposure to this metabolite still occurs. DDT is a well-established reproductive toxin in some wildlife species, but the effects of DDT on reproduction in humans are unclear and not well studied. Some studies have linked DDE to preterm birth, but these were small studies and the results were not conclusive.

Advance: Investigators measured concentrations of the DDT metabolite, DDE, in 2,613 serum samples originally taken from pregnant mothers enrolled in the 1960s in the U.S. Collaborative Perinatal Project. These researchers found that the mothers exposed to DDE were more likely to give birth prematurely, and to babies who were unusually small. Premature birth is a major risk factor for infant mortality.

Implications: Because use of DDT for malaria control is ongoing in 25 countries, the new findings should affect considerations regarding use of pesticides in those countries. Benefits of mosquito vector control with DDT might need to be reassessed in light of these data and in conjunction with the availability of alternative methods of pest management.

Longnecker MP, Klebanoff MA, Zhou H, and Brock JW: Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. Lancet 358: 110-114, 2001.

Modest Increases in Ambient Ozone Concentration are Associated with Increases in School Absenteeism

Background: Poor air quality is widely recognized as a risk factor for causing or exacerbating pulmonary diseases such as asthma. Ozone (O₃), nitrogen dioxide (NO₂), and particulate matter less than 10 mm in diameter (PM₁₀) are known to contribute to temporary changes in lung function, increased risk of respiratory infections, more visits to physicians and emergency rooms, increased hospital admissions, and increased mortality. The economic impact of these illnesses is staggering when medical expenses and lost work productivity are taken together. School absenteeism is an important but poorly understood adverse outcome in children causing missed learning opportunities and the inability of the children to fully participate in school activities. The National Asthma Education and Prevention Program, the President's Task Force on Environmental Health Risks and Safety Risks to Children, and the Department of Health and Human Services Asthma Workgroup have all targeted school absenteeism as a high priority problem in the fight against asthma.

Advance: This paper describes an investigation of the relationships between O₃, NO₂, PM₁₀, and school absenteeism during the first 6 months of 1996 in a group of 4th grade children living in 12 southern California communities. The pollutants were measured hourly at monitoring sites in each of the 12 communities. Short-term change in O₃ was associated with substantial increases in school absences from both upper and lower respiratory illnesses. An increase of 20 ppb (parts per billion) of daytime O₃ was associated with increases of 62.9% in illness-related absentee rates, 82.9 percent for respiratory illnesses, 45.1 percent for upper respiratory illnesses, and 173.9 percent for lower respiratory illnesses with cough. The short-term effects of the O₃ increase on illness-related absenteeism were larger in communities with lower average PM₁₀ concentrations than communities with high average PM₁₀.

Implications: This study demonstrates that relatively small changes in O₃ are associated with increases in respiratory illnesses and subsequent school absenteeism in 9-10 year old children. The level of exposures observed in this study are common, suggesting that the increases in school absenteeism resulting from respiratory illnesses associated with relatively modest changes in ambient O₃ concentration are also common. This result documents an important adverse impact on children's health and well-being.

Gilliland FD, Berhane K, Rappaport EB, Thomas DC, Avol E, Gauderman WJ, London SJ, Margolis HG, McConnell R, Islam KT, and Peters JM: The effects of ambient air pollution of school absenteeism due to respiratory illnesses. Epidemiology 12: 43-54, 2001.

Variations in the Gene for Microsomal Epoxide Hydrolase: Possible Answer to "Why Me?"

Background: One of the most puzzling questions in medicine and science is why people with similar environments and life-styles have differences in cancer incidence. For instance, why do some smokers develop lung cancer and others remain cancer free? One probable reason is differences in genetic makeup.

Colon cancer has been linked in several research studies to exposure to polycyclic aromatic hydrocarbons (PAHs), chemicals found in cigarette smoke and in meats cooked well-done. The potential for these compounds to cause cancer may be dependent on the length and amount of exposure and their activation or inactivation by metabolic enzymes. Different variations, or polymorphisms, in the genes coding for these enzymes have been found. A person may be more or less susceptible to the carcinogenic effects of PAHs depending on which polymorphisms they have in their genetic make-up, especially in the genes coding for a variety of important enzymes.

Advance: This report focuses on polymorphisms in the gene for microsomal epoxide hydrolase (mEH), an enzyme involved in PAH metabolism. Among individuals who have high mEH enzyme activity, smoking and consumption of well-done red meat were significantly associated with the presence of colon adenoma. Differences in inactivation and excretion of PAHs due to mutations in glutathione S-transferase M3 may also be involved.

Implications: These results suggest that mEH activity is associated with a risk for colorectal adenomas when environmental exposures and other response-mediating genes are taken into account. They also suggest that at least part of the increased risk for adenoma is associated with smoking and the consumption of well-done red meat. Both lifestyle factors are consistent with PAH exposure. This paper illustrates how gene regulation of enzyme activity may at least partially explain differences in disease state and exposure response in people living in similar environments.

Cortessis V, Siegmund K, Chen Q, Zhou N, Diep A, Frankl H, Lee E, Zhu QS, Haile R, and Levy D: A case-control study of microsomal epoxide hydrolase, smoking, meat consumption, glutathione S-transferase M3, and risk of colorectal adenomas. Cancer Research 61: 2381-2385, 2001.

Amphibian Deaths Linked to Global Climate Change

Background: One of the major obstacles in studying ecological or health effects of global climate change is establishing links between seemingly disparate meteorological and biological events. This report is the first to suggest global climate change as a cause of amphibian population decline in the western U.S. Scientists have been reporting declines in worldwide amphibian populations since the late 1970s. There have been reports in the scientific and lay media about frog deformities as well, but the causes of these events have been elusive.

Advance: Researchers have linked extremely dry climatic events and ultraviolet radiation with infection of toad eggs by *Saprolegnia ferax*, a water-borne mold pathogen. They have discovered that El Niño-induced warming of the Pacific Ocean causes dryer than normal conditions in the Cascade mountains. Dry conditions cause lakes where amphibians reproduce to be shallower than normal, which in turn causes the amphibian eggs to be closer to the water's surface where they are exposed to higher levels of ultraviolet-B radiation (UV-B). UV-B radiation weakens the immune system in the developing embryos making them more susceptible to infection by *S. ferax* which is the ultimate cause of death. *S. ferax* generally only presents a risk to organisms that are injured or under stress. Experiments where the depth of the water is controlled produce healthy toads, but this group reports mortality of up to 100 percent in shallow conditions.

Implications: This research documents an interesting paradigm in which an environmental toxicant, in this case UV radiation, can weaken an immune system leading to opportunistic infections. The finding serves as a warning that global climate changes are having effects on biodiversity and the health of ecosystems. It also suggests that other population declines may not only be caused by habitat destruction or natural population flux. Finally, the results offer evidence that to avoid potentially high losses of biodiversity, cleaner, more sustainable energy options need to be stressed by policy makers.

Kiesecker JM, Blaustein AR, and Belden LK: Complex causes of amphibian population declines. Nature 410: 681-684, 2001.

In utero and Postnatal Exposure to Polybrominated Biphenyls Causes Early Puberty in Girls

Background: In 1973, an accidental contamination of animal feed in Michigan caused human exposure to a class of compounds, the polybrominated biphenyls (PBB). The PBB-containing fire retardant Firemaster was inadvertently added to livestock feed in place of a magnesium supplement. In the months following, many Michigan residents ate animal and dairy products that had been contaminated. After discovery of the contamination, a registry of exposed individuals was established in 1976.

Maternal ingestion of PBB and polychlorinated biphenyls leads to exposure of the fetus through the placenta and to infants via breastfeeding. PBB rodent studies demonstrated effects on the reproductive system of female pups from exposed mothers. These studies suggest that exposure to PBB during gestation and early infancy may alter hormonal signaling pathways necessary for proper growth and maturation. The present study evaluates the association between perinatal (occurring before, during, or after birth) PBB exposure and subsequent age of first menstrual period, breast development, and pubic hair development in daughters of women exposed to PBB.

Advance: Breastfed girls exposed to high levels of PBB *in utero* (>7 parts per billion) had an onset of first menstruation one-half to one year earlier than breastfed girls exposed to lower levels of PBB (11.6 years vs. 12.2-12.6 years respectively). Perinatal PBB exposure also caused earlier pubic hair development in breastfed girls but little association was found with breast development. A possible mechanism of action may involve the thyroid gland. The main PBB component of Firemaster is known to affect thyroid hormone concentrations. Normal pubertal development is partially dependent on thyroid hormones. Other animal studies have shown that exposure to PBB during pregnancy and lactation causes decreased thyroxine levels in neonates. Five of the 327 daughters in this study have reported thyroid problems, and all five were born within a few years of the incident (1974-1976)..

Implications: The associations reported from this research lend support to the hypothesis that *in utero* and lactational exposure to PBB have profound effects on normal pubertal development. The reports of thyroid dysfunction suggests the possibility of thyroid involvement as a mechanism of action and opens a new line of investigation for future epidemiologic and animal studies. Although the exposures in this study were accidental, the results have a broader application because numerous environmental contaminants have been shown to have endocrine disrupting abilities like the PBBs. The general population has exposures at much lower concentrations than in this study, but the potential for long-term effects illustrated by these results raises important regulatory issues for environmental endocrine-disrupting compounds.

Blanck HM, Marcus M, Tolbert PE, Rubin C, Henderson AK, Hertzberg VS, Zhang RH, and Cameron L: Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. Epidemiology 11: 641-647, 2000.

Risk Factors for Asthma Identified

Background: Asthma is a chronic lung condition characterized by extreme shortness of breath or inability to breathe. In the U.S., rates of asthma deaths, hospitalizations, and emergency room visits have been increasing for more than two decades, especially among African-Americans and children. Asthma costs this Nation approximately \$14 billion each year¹. Uncovering environmental triggers of this disease and its potential susceptibility factors would help prevent many new cases and help prevent more asthma attacks in current patients.

Advance: Risk factors for asthma have generally considered childhood asthma as a single entity. It has recently been appreciated that the development of asthma may differ according to the age at onset and persistence into later childhood. Few data have been presented in this way. These researchers found that family history of asthma and allergy was most strongly associated with early onset asthma that persists past early childhood, confirming two previous findings. In a novel analysis, they further found that an early life exposure, maternal smoking in pregnancy, was most strongly related to risk of this most serious asthma entity among children with a parental history of asthma or allergy. This finding suggests that early life exposure may produce the most long lasting harm in genetically predisposed children. This finding could have implications for the study of other early life exposures in asthma.

Implications: This study uncovers a preventable asthma initiator, maternal smoking in pregnancy, for the most serious and persistent type of childhood asthma. If translated into national prevention efforts, it could help reduce new cases of this disease among children.

London SJ, Gauderman WJ, Avol E, Rappaport E, and Peters JM: Family history and the risk of early onset persistent, early onset transient and late onset asthma. Epidemiology - (in press 2001).

¹“Costs of Illness and NIH Support for Selected Diseases and Conditions” - Part 1A.

Are Plasticizers in the Environment Making You Infertile?

Background: A number of chemicals released into the environment have the potential to be hormonally active and to disrupt endocrine and reproductive functions. These chemicals include pesticides such as DDT (no longer allowed in this country), its persistent by-product, DDE, and a group of compounds used to make plastics flexible, the phthalates. Although we currently know that wildlife, if exposed to high levels, can be adversely affected, we are still learning about possible effects in humans and the consequences of low-dose exposures. One chemical of concern is di-(2-ethylhexyl) phthalate, which is manufactured in the amount of a million tons per year to enhance plastics and then ends up as a common environmental contaminant.

Advance: Di-(2-ethylhexyl) phthalate disrupts endocrine and reproductive function in model species by preventing ovulation leading to infertility. Scientists now report that the active metabolite of this phthalate affects the ovary by altering levels of aromatase, an enzyme responsible for making the female hormone estradiol. Because the steps involved in hormone production are very similar in rodents and humans, this work may help in understanding how this chemical affects reproductive function in women.

Implications: Understanding the molecular mechanism of phthalate action helps us better define the probable health outcomes of these exposures, as well as helping to develop biomarkers for use in epidemiologic studies on the health risks of these compounds.

Lovekamp TN, and Davis BJ: Mono- (2-ethylhexyl) phthalate suppresses aromatase transcript levels and estradiol production in cultured rat granulosa cells. Toxicology and Applied Pharmacology 172: 217-224, 2001.

Genistein, a Plant Estrogen Found in Soy Products, Increases Cancer in Animals

Background: The developing fetus is uniquely sensitive to perturbation by estrogenic chemicals. The potent synthetic estrogen, diethylstilbestrol (DES), for example, causes cancer in both rodents and people exposed early in life. The environment contains a number of weakly estrogenic compounds and the role of early exposure to these chemicals on later cancer risk is of concern. One such compound is genistein which is found in plants such as soy. Early exposure to this compound could occur if a woman ingests a large number of soy products during her pregnancy or uses a soy-based infant formula for her child.

Advance: A new animal study reports that treatment with genistein during development causes cancer of the reproductive tract later in life. Scientists observed an increase in cancer of the uterus in aged female mice treated with genistein under the skin for only 5 days after birth. Thus, very early exposure to this compound caused cancer development later in the animal's life.

Implications: Humans are exposed to high levels of genistein during development through the use of soy-based infant formulas and soy products marketed specifically to appeal to children. The use of soy-based infant formulas in the absence of medical necessity and the marketing of soy products designed to appeal to children should be closely examined.

Newbold RR, Banks EP, Bullock B, and Jefferson WN: Uterine adenocarcinoma in mice treated neonatally with genistein. Cancer Research 61: 4325-4328, 2001.

Two Dietary Plant Estrogens Increase Cancer Risk in Mice

Background: Our diet contains a number of naturally occurring compounds that can either mimic or compete with the hormone estrogen. Products derived from the soybean are particularly high in two of these compounds, daidzen and genistein. Soybeans are a major protein source in vegetarian diets and many women consume soy products to reduce hot flashes and other symptoms of menopause. Given the biological activity of plant estrogens (phytoestrogens), the potential exists for adverse, as well as beneficial, health effects.

Advance: Researchers discovered that phytoestrogens in the diet increased the incidence of vulvar carcinoma in mice. Mice were given one of three natural ingredient diets or two purified diets containing predetermined levels of the phytoestrogens, daidzein and genistein. The two purified diets had similar caloric values and differed only in their protein source – derived from either soy protein or milk protein (casein). At three months, mice on the soybean-supplemented diet had a significantly increased incidence of vulvar carcinomas compared to mice fed a milk-derived protein source. A similar correlation was found between tumor incidence and phytoestrogen levels in the three natural ingredient diets. In total, there was a significant correlation between the total daidzein and genistein levels in the five test diets and the incidence of vulvar carcinomas in mice.

Implications: Many consumers think that a “natural” diet is a safe diet. In fact, as this study shows, the reality is more complicated and ingesting too much of some phytoestrogens may potentially increase cancer risks. Consumers need to exercise caution and to consume a varied diet with multiple sources of protein in order to safeguard their health.

Thigpen JE, Locklear J, Haseman JK, Saunders H, Grant MF, and Forsythe DB: The effects of the dietary phytoestrogens daidzein and genistein on the incidence of spontaneous vulvar carcinomas in 129/J mice. Cancer Detection and Prevention (in press 2001).

Simple Steps Can Reduce Dust Mite Allergen Exposure in Low Income, Urban Homes

Background: Asthma is a serious lung disease that disproportionately affects inner-city, lower socioeconomic status individuals. Dust mite allergen exposure is an important risk factor for asthma development; however the best methods to reduce exposure to this allergen in low income, urban homes remain unknown. A study was initiated to identify effective and useful remedies that could be implemented in low-income communities to reduce environmental triggers of asthma in homes.

Advance: This study showed that using impermeable mattress/pillow covers in combination with weekly laundering of bedding significantly reduces dust mite allergen exposure in the bed. Moreover, steam cleaning of bedroom carpets together with vacuuming reduces dust mite allergen levels in bedroom floors. Simple, practical interventions may provide effective means for reducing dust mite allergen exposure in high risk environments.

Implications: In an era of high-tech, high-cost medicine, simple prevention methods can sometimes be overlooked. This study identifies effective methods for removing environmental triggers of asthma from the home. These methods are not only effective, but also inexpensive and within the ability of the average homeowner to achieve. If implemented, these techniques could result in significantly reduced costs of asthma treatment and, more importantly, significantly reduced morbidity and mortality from asthma attacks.

Vojta PJ, Randels SP, Stout J, Muilenberg M, Burge HA, Lynn H, Mitchell H, O'Conner GT, and Zeldin DC: Effects of physical interventions on group I house dust mite allergen levels in carpet, bed, and upholstery in inner city homes. Environmental Health Perspective 109: 1-5, 2001.

The Effects of Implant Wear Particles on Bone Cells

Background: Total joint replacement has been shown to be a very effective treatment for disabling end-stage arthritis of the hip and knee. Recent studies have shown that the major cause of failure of these treatments today is “periprosthetic osteolysis,” the literal disappearance of bone around an implant because of a reaction precipitated by minute plastic and metal wear particles. The particles were initially thought to only affect osteoclasts (normal bone cells that aid in bone remodeling through the dissolution of bone), but previous work revealed that these wear particles also directly affect osteoblasts (another normal bone cell that functions to make new bone). In particular, they showed that wear particles cause osteoblasts to activate osteoclasts (increased disappearance of bone) and to decrease the formation of new bone (through decreased collagen production).

Advance: The purpose of this study was to further define the direct effects of wear particles on osteoblasts. Through a series of experiments, researchers verified that these wear particles do directly affect osteoblasts, with a resultant decrease in new bone formation. In addition, they found that osteoblasts are also affected by normal chemicals in the body that stimulate growth. In particular, two of these normal chemicals called growth factors, IGF-1 and TGF β -1, were shown to stimulate new bone formation in the presence of these wear particles.

Implications: Much of the current research to find ways to prevent osteolysis center on osteoclasts and the mechanism(s) of bone dissolution around the implant. The use of certain growth factors and some existing medications used to treat osteoporosis have been proposed to “turn off” this bone loss. These findings point to a new possible point of attack, the osteoblast. If further validated, the local delivery of certain growth factors (i.e., IGF-1 and TGF β -1) into the area of osteolysis, could be a treatment option by stimulating new bone formation. This could result in new treatments to treat or prevent bone loss around an orthopaedic or dental implant.

Vermes C, Chandrasekaran R, Jacobs JJ, Galante JO, Roebuck KA, and Glant TT: The effects of particulate wear debris, cytokines, and growth factors on the functions of mg-63 osteoblasts. The Journal of Bone and Joint Surgery 83-A: 201-211, 2001.

Molecular and Psychological Influence on Barrier Function of Skin

Background: The outermost layer of the skin, the stratum corneum, functions as a barrier to prevent external molecules from entering our bodies as well as preventing water and other molecules from leaving the body. There has been much research as to the particular components that function as the main barrier to molecules in the stratum corneum, and also which external influences result in abnormalities of this function. Stress has been often cited by patients as causing or exacerbating skin disease and, recently, there has been some research examining neurotransmitters (molecules produced at the nerve endings when the nerve is activated) for their influence on epithelial structure and function. This has recently extended to investigations of the effects of stress on the stratum corneum barrier function.

Advance: One group of investigators examined molecules involved in the formation of the stratum corneum in mice by knocking out a molecule, loricrin, the major structural protein in the stratum corneum, comprising 70 percent of this structure by mass. When mice deficient in the molecule were developed using transgenic technology, their stratum corneum was somewhat more fragile but still had normal barrier function. Even the fragility disappeared by 4 or 5 days of life. In other studies, stress levels and barrier function were assessed in medical, dental and pharmacy students without skin disease. The recovery of barrier function following specific tests was retarded in proportion to the level of stress being experienced by the individuals. Barrier recovery was faster in the same individuals during periods of low stress compared to periods of high stress. This is the first demonstration in humans that stress has a biologic effect on the skin's barrier.

Implications: These two studies at opposite ends of the spectrum, transgenic molecular models versus intact human investigations, demonstrate that the barrier function of the stratum corneum is the end result of a complex series of events. There are compensatory mechanisms that allow restoration of normal barrier even in the absence of major normal structural proteins. However, even when there are no obvious physical abnormalities, psychological stress can result in impaired barrier function. All levels of barrier function need to be studied to fully understand this function and to devise the safest and most effective interventions to restore barrier function when it is disrupted because of diseases and other conditions.

Garg A, Chren MM, Sands LP, Matsui MS, Marenus KD, Feingold KR, Elias PM: Psychological stress perturbs epidermal permeability barrier homeostasis: Implications for the pathogenesis of stress-associated skin disorders. Archives of Dermatology 137:53-59, 2001.

Koch PJ, de Viragh PA, Scharer E, Bundman D, Longley MA, Bickenbach J, Kawachi Y, Suga Y, Zhou Z, Huber M, Hohl D, Kartasova T, Jamik M, Steven AC, Roop DR: Lessons from loricrin-deficient mice: compensatory mechanisms maintaining skin barrier function in the absence of a major cornified envelope protein. Journal of Cell Biology 151:389-400, 2000.

Osteoarthritis in Young and Middle-aged Women

Background: Osteoarthritis is a slowly evolving degenerative disease affecting cartilage and bone that may appear at different sites. Because osteoarthritis has been considered a disease of the elderly, few studies have been carried out in persons under the age of 45.

Advance: Investigators at a research center examined X-rays of both knees and the dominant hand in a population of younger African-American and Caucasian women in southeastern Michigan. They found that the prevalence of osteoarthritis of the knee increased over ten-fold to 15 cases per 100 women ages 40-44 from 1.34 cases per 100 women ages 35-39. Osteoarthritis of the hand was found in 10 percent of women over 40 years of age but only in 1 percent of those younger than 40. Osteoarthritis of the knee was 2.7 times more frequently found in African-American women over 40 years of age than in Caucasian women. Body mass index (BMI) has been found to be a risk factor for osteoarthritis. In this study, the odds of having osteoarthritis of the hand increased 56 percent for every 10 unit increase in BMI while the odds of having osteoarthritis of the knee increase by 14 percent for every 10 unit BMI increase.

Implications: This study demonstrates that signs of osteoarthritis of the hand and knee are common in women. The emergence of osteoarthritis occurs rapidly between 35 and 40 years. This study provides strong evidence that primary prevention of osteoarthritis must be implemented in young adulthood to curtail the emergence of osteoarthritis in mid-life.

Sowers M, Lachance L, Hochberg M, and Jamadar D: Radiographically defined osteoarthritis in the hand and knee in young and middle-aged African American and Caucasian women. Osteoarthritis and Cartilage 8: 69-77, 2000.

Effect of Dietary Protein on Bone Loss in Elderly Men and Women: The Framingham Osteoporosis Study

Background: The role of protein in bone metabolism is an area of some controversy. Dietary protein (particularly that from an animal source when there is a high level of sulphur amino acids) can cause an increased acid load, which results in the transfer of calcium from bone to maintain acid-base balance. Many laboratory studies have shown that high protein intake is an important and powerful determinant of urinary calcium loss, which can in turn cause negative calcium balance and hence an increase in bone loss. However, other studies have shown that protein under-nutrition is associated with osteoporosis and that low protein intake or even protein "insufficiency" is particularly associated with frailty and fracture in the elderly population.

Advance: The relationship between dietary protein intake and 4-year change in lumbar spine, femoral neck, and radial shaft BMD (bone mineral density) was examined as part of the population-based, Framingham Osteoporosis Study. Subjects included 391 women and 224 men, and the mean age at baseline was 75 years. Usual dietary protein intake was assessed using a semiquantitative food frequency questionnaire, and results were expressed as a percent of energy from protein intake. Statistical analysis of protein:bone loss relationships was performed after adjustment for important confounding factors, which included age, weight, height, smoking, alcohol and caffeine consumption, and current estrogen use for women.

Results indicated that lower protein intake was significantly associated with greater bone loss at the spine and femur skeletal sites but not the radial shaft (leg), with subjects in the lowest quartile of protein intake showing the highest level of bone loss. Results were consistent after adjustment for important confounding factors, which included body weight loss. The two key findings from this study were, first, that protein intake was found to be important in maintaining skeletal health in the elderly population, and second, a higher intake of animal protein did not appear to have any detrimental effects on skeletal integrity.

Implications: This is an important study concerning the role of diet (particularly protein nutrition) on bone health maintenance of the aging population. Results strongly suggest that adequate protein intake is related to reduced bone loss, and no evidence of a deleterious effect of high animal protein consumption on skeletal health was found. The results of this study should encourage an adequate consumption of dietary protein in the elderly population and point to the potential benefits of this on skeletal health.

Hannan MT, Tucker KL, Dawson-Hughes B, Cupples LA, Felson, DT and Kiel DP: Effect of Dietary Protein on Bone Loss in Elderly Men and Women: The Framingham Osteoporosis Study. Journal of Bone and Mineral Research 15: 2504-2512, 2000.

Jumping Improves Hip and Spine Bone Mass in Prepubescent Children: A Randomized Controlled Trial

Background: Developing a stronger skeleton in childhood is an extremely important mechanism to prevent osteoporosis in later life. Exercises that produce impact on bone have been shown to be more effective in increasing peak bone mass (bone mineral content [BMC]) than other types of low-impact activity. For example, there is good evidence in the literature that gymnasts exhibit higher levels of bone density compared with age-matched controls. Gymnastic activities often expose the athlete to ground reaction forces of 10-15 times body weight.

Advance: These investigators designed a 7-month high-intensity jumping regimen that could be implemented in a regular elementary school curriculum and developed ground reaction forces of eight times body weight. The effect of jumping on hip and spine bone mass was investigated in 89 prepubertal children between the ages of 5.9 and 9.8 years. Male and female subjects were randomized into either a jumping group or control group. The exercise involved participation during the school day 3 times per week and involved 100 two-footed jumps off 61-cm-high boxes at each session. The control group participated in nonimpact stretching exercises.

Bone mineral density (BMD), bone mineral content (BMC), and bone area were assessed at the hip and spine by dual x-ray absorptiometry. Differences in indices of bone health between the 2 groups were analyzed, controlling for initial age, bone values, and changes in both weight and height. The jumping group was found to have a significantly greater 7-month change in BMC at both the hip and spine than controls (4.5 percent versus 3.5 percent); similar (although slightly lower) results were seen for both the BMD and bone area analyses.

Implications: This study has important public health implications with respect to optimizing peak bone mass attainment in young individuals. A simple jumping program offered in the prepubertal years may increase peak bone mass at 2 clinically relevant sites, the hip and spine. Such a regimen appeared both safe and effective and clearly is a program of exercise that could be incorporated into physical education programs of primary and secondary schools.

Fuchs RK, Bauer JJ, and Snow CM: Jumping Improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial. Journal of Bone and Mineral Research 16: 148-156, 2001.

How are Mental Disorders and Violence Related?

Background: Much of the stigma attached to mental illness stems from perceptions that persons with a mental illness have an unpredictable and indiscriminate propensity for violent behavior. In fact, the majority of individuals with a mental disorder are not violent, much less convicted of a violent crime; conversely, the vast majority of convicted offenders have no history of a psychiatric disorder.

Advance: NIH-funded investigators examined data on 961 young adults from a total-city birth cohort in New Zealand born in 1972-3. Because most people with mental disorders are not hospitalized, and most violent individuals are not convicted of crimes, the investigators chose this sample with no regard to their contact with the health and justice systems. The prevalence of mental disorders was measured using standardized DSM-III-R psychiatric diagnostic interviews, and violence was measured using self-reports of criminal offending and a search of official conviction records. The researchers found that young adults meeting diagnostic criteria for alcohol dependence, marijuana dependence, and schizophrenia-related disorder were 1.9, 3.8, and 2.5 times respectively, more likely than control subjects to be violent. People with at least one of these three disorders constituted one-fifth of the sample, but they accounted for one-half of the sample's violent crimes (10 percent of violence risk was uniquely attributable to schizophrenia-spectrum disorder). People with two of these disorders simultaneously carried a risk for violence that was 8 to 18 times greater than that for individuals with no disorders. Among alcohol-dependent individuals, violence was best explained by alcohol use hours before the offense; among marijuana-dependent individuals, by a juvenile history of conduct disorder; and among individuals with schizophrenia-related disorder, by excessive perceptions of threat and a history of conduct disorder. Only 8.1 percent of the 389 cohort members with one or more mental disorders were taking psychiatric medications, and only 3.1 percent had been hospitalized in the past year.

Implications: These findings suggest that a substantial proportion of the burden of violence that alarms and injures the general public may be attributed to a limited number of young adults who are prone to schizophrenia-spectrum disorders or dependent on alcohol or other drugs and are untreated. Moreover, because each disorder was linked to violence through different core explanations, each has different potential implications for treatment and prevention. For individuals with schizophrenia-spectrum disorders, for example, cognitive therapy or medication that reduces threat perceptions might reduce violence. More broadly, these findings imply that the link between adult mental disorders and violence is often rooted in certain aspects of childhood and adolescent conduct problems, and thus may be amenable to primary prevention.

Arseneault L, Moffitt TE, Caspi A, Taylor PJ, and Silva PA: Mental disorders and violence in a total birth cohort: results from the Dunedin Study. Archives of General Psychiatry 57: 979-986, 2000.

Preventing Chronic Depression and Substance Abuse

Background: For many people, depression is a chronic, recurrent disorder associated with a variety of other health problems, including substance abuse. Research in community populations is providing increasing evidence that major depressive disorder (MDD) is one of the most common mental disorders in adolescence, precedes the onset of many other disorders, and is unlikely to be outgrown.

Advance: Having MDD in adolescence places individuals at significant risk for recurrent depressive episodes, other disorders (particularly substance abuse disorders), and impaired functioning. The Oregon Adolescent Depression (OADP) Study began in 1987 with mental health assessments of 1,709 adolescents ages 14-18. Since then, there have been three waves of psychiatric assessments and a family psychiatric history study. In the OADP sample, of those who had experienced an episode of major depressive disorder by age 19, one-fourth experienced subsequent pure major depressive disorder by age 23, one-fourth experienced comorbid major depressive disorder, and one-fourth remained free from depression but experienced a non-mood mental disorder (primarily a substance abuse disorder). Thus, only one-fourth of the depressed youth were free of mental disorder by age 23. Because most of the episodes of non-mood disorder began after age 19, the sequence and timing of these disorders seem to be critical. These data are consistent with previous reports suggesting a window of several years between the onset of depression and new disorders, as well as a progression from depression into substance abuse.

Implications: This study underscores both the urgent need for early and better identification and treatment of depressed adolescents as a way to avoid a protracted course of disorder and dysfunction in adulthood. At present, only a small proportion of adolescents with depression are recognized and treated. Systematic, controlled treatment studies are essential to determine whether appropriate treatment in adolescence can alter long-term morbidity and adaptation. The early detection and effective treatment of adolescents with depression may provide an important window of therapeutic opportunity and help reduce the future burden of substance abuse as well as other mental disorders.

Lewinsohn PM, Rohde P, Seeley JR, Klein DN, and Gotlib RN: Natural course of adolescent major depressive disorder in a community sample: predictors of recurrence in young adults. American Journal of Psychiatry 157(10):1584-1591, 2000.

Negative Impact of Parental HIV Illness Can Be Prevented in Their Children

Background: An increasing number of HIV-infected parents in the U.S. face a painful prospect: living with a chronic, life-threatening illness or dying prematurely. How well HIV-infected parents can take care of their families as well as their illness is likely to influence their children's long-term development and well-being. After living with an ill parent, about 80,000 children in the U.S. have been orphaned by AIDS. Their loss of a parent can reduce their self-esteem and increase depression, anxiety, conduct disturbance, academic difficulty, somatic complaints, and suicidal acts. However, there has been little prospective research on children of parents with long-term chronic diseases – particularly adolescent children – to guide preventive efforts. Scientists now are addressing that knowledge gap by assessing an intervention with a unique population of 307 single Latino and African-American women with AIDS and their 412 adolescent children. Subjects are assigned either to a “standard care” control condition or to an intensive intervention designed to improve behavioral and mental outcomes for both adolescents and their parents. The intervention was offered in two modules to small groups at a community center. Module 1 sessions, for parents, focused on coping with illness, fear, anger, sadness, and the meaning of illness, as well as disclosure decisions and planning for the future. Module 2 sessions, for parents and adolescents, focused on planning a legacy, including making custody arrangements, resolving home conflicts, dealing with drugs, encouraging safer sex, and setting future goals. (Control group participants were visited by an interviewer every 3 months and asked about disclosure, custody, and risk behaviors.). Over the study's 2- year course, 44 percent of the parents in both groups died, and a third intervention (still being evaluated) was given to help the bereaved adolescents and their caregivers.

Advance: Compared to controls, adolescents in the intensive intervention program reported significantly lower levels of emotional distress, multiple problem behaviors, conduct problems, and family-related stressors, as well as higher self-esteem. Parents with AIDS also reported significantly lower levels of emotional distress and multiple problem behaviors. The effects were typically large. While problem behaviors increased or remained stable in the non-intervention families, there were significant decreases among both the parents and the adolescents who received the intervention. At two years, intervention-group adolescents reported four times fewer problem behaviors and 2.4 times fewer conduct problems than their control-group peers. Increases in self-esteem were also evident, and multiple problem behaviors decreased at a higher rate among the intervention-group parents. However, coping styles, levels of disclosure about serostatus, and parental initiative in making legal custody plans were similar for the intervention and control groups. Also, in this study, as in every major HIV prevention trial, sustained (but lesser) improvements were also seen in the control group – in this case, an improvement over time in emotional distress.

Implications: This study provides important evidence that a well-designed intervention can reduce the adverse impact of parents' HIV status on themselves and their children. The intervention resulted in important, long-term changes that could, if more broadly implemented, reduce the societal costs of AIDS. Further replication of this manualized intervention is needed to establish its transferability and its cost-benefits.

Rotheram-Borus MJ, Lee MB, and Gwadz M: An intervention for parents with AIDS and their adolescent children. American Journal of Public Health 91: 1303-1309, 2001.

Protecting the Brains of Infants During Surgery for High-risk Heart Defects

Background: Each year about 30,000 infants in the U.S. are born with congenital heart disease and at least a third need surgery during infancy. In hypoplastic left heart syndrome (HLHS) the heart is severely underdeveloped and unable to pump enough blood. HLHS was invariably fatal until surgeons developed methods to repair the defect in the 1980's. Since then, survival rates have been improving, but neurological damage often occurs due to the stress of the surgery, which requires stopping the heart, cardio-pulmonary bypass, lowering the infant's body temperature, and then reversing the procedure, which itself has risks. One hypothesis about what causes damage is that the procedures increase the generation of free radicals. Free radicals are highly reactive chemicals suspected of damaging the heart and brain in many acute events, such as stroke and trauma, as well as in chronic diseases, such as Parkinson's and ALS.

Advance: Research has now demonstrated that the drug allopurinol helps reduce the risks of surgery in infants with HLHS. Allopurinol is widely used to treat gout in adults. The researchers chose the drug because it may scavenge or inhibit the formation of free radicals. The study was a 5 year, randomized, placebo controlled, blinded clinical trial. That is, infants undergoing surgery were randomly assigned to a group that received the drug or a group that received a placebo. Doctors and caretakers did not know which infants received the drug, so they could not unconsciously bias the results. And all infants received the best possible care, except for the as yet untested drug. When the results were available, infants treated with allopurinol had fewer seizures and cardiac events, such as reduced heart rate and respiration, indicating that the drug had significant protective effects.

Implications: The most direct implication is that the drug allopurinol may help protect infants undergoing surgery for HLHS. Future trials may identify neuroprotective drugs that help infants undergoing surgery for other heart defects for which allopurinol did not seem to work in this trial. Although finding ways to protect infants during surgical procedures is in its own right important, the potential implications are much broader. Finding effective neuroprotective agents is crucial for many circumstances – birth asphyxia, bypass surgery in adults, stroke and trauma, and many chronic disorders. The unfortunate circumstances of infants who need high-risk surgery for severe problems offers advantages, compared with unexpected events like birth problems or stroke, for evaluating neuroprotective agents that may have more general applications.

Clancy RR, McGaurn SA, Goin JE, Hirtz DG, Norwood WI, Gaynor JW, Jacobs ML, Wernovsky G, Mahle WT, Murphy JD, Nicolson SC, Steven JM, and Spray TL: Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. Pediatrics 108: 61-70, 2001.

Another (Running) Step Towards Protecting the Brain in Ataxia-Telangiectasia

Background: Children with ataxia-telangiectasia (A-T) develop normally at first, then suffer from progressive brain dysfunction and usually die by their teens or twenties. A-T also can result in poor immune function, diabetes, retarded body growth, premature aging, predisposition to malignancies, and extreme sensitivity to radiation. In 1995, scientists identified the gene (ATM) that, when mutated, causes A-T. Subsequent research found that ATM is a protein kinase, a type of enzyme that regulates the activity of other proteins. The normal ATM protein helps control molecules that arrest cell division and initiate cells' repair systems when DNA is damaged. This helps explain the sensitivity to radiation and tendency for malignancies to develop when the ATM protein malfunctions in A-T and has led to research that implicates ATM in cancer more generally. However, why mutations in ATM lead to the progressive and fatal neurodegeneration of A-T is not at all clear.

Advance: To investigate how defects in ATM might affect the brain, scientists capitalized on recent findings about the generation of new nerve cells in the brain. A series of groundbreaking experiments have shown that parts of the adult brain continue to generate new nerve cells. Furthermore, behavior and environmental stimuli, such as exercise, affect the proliferation and survival of the new cells. One brain area that continues to generate new cells is the dentate gyrus of the hippocampus, which is crucial for the formation of new memories. The research team investigated mice engineered to be deficient in ATM. In these mice, new cells in the dentate gyrus arose at higher rates than normal, but the rate did not respond as strongly to running, which normally stimulates proliferation and survival of new cells. Another difference was that most new cells in the ATM-deficient mice were supporting cells, called astrocytes, rather than nerve cells. The additional finding that the ATM protein is normally abundant in dividing cells, but not in cells that are specialized, fits well with this scenario. Although the details are not entirely worked out, ATM's role in maintaining the integrity of the genome may point to the mechanism of these effects.

Implications: The most direct implication for children with A-T is the novel suggestion that finding an appropriate environment, whether through exercise or other stimuli that affect cell proliferation, may slow the course of the disease. More generally, ATM seems to be critical for allowing brain cells to respond appropriately to cues from the environment that influence survival and specialization. In the long run, understanding how to encourage brain cell proliferation and survival may be important for treating many diseases of the brain.

Allen DM, van Praag H, Ray J, Weaver Z, Winrow CJ, Carter TA, Braquet R, Harrington E, Reid T, Brown KD, Gage FH, and Barlow C: Ataxia telangiectasia mutated is essential during adult neurogenesis. Genes and Development 15: 554-566, 2001.

Dietary Supplement for Brain Injury and Disease

Background: Impaired energy metabolism has been implicated in several types of neurological dysfunction, including stroke, Huntington's disease (HD) and traumatic brain injury. Because of the prevalence and severity of these conditions, researchers are directing considerable efforts toward identifying agents that can protect neurons from damage caused by temporary energy deficiencies.

Creatine is a common food supplement that is especially favored by athletes since it is present in muscle at high concentrations, where it serves as an energy source during heavy exercise. Creatine supplementation of the diet also increases concentrations in the brain. Just as it can provide a needed energy-buffer in overworked muscle, creatine may protect energy-deprived neurons from damage caused by brain injury or disease.

Advance: Chronic administration of creatine reduced brain damage from experimental traumatic injury by more than one-third in mice and by about one-half in rats. In a separate study, the diet of transgenic mice expressing the Huntington disease protein was supplemented with creatine. The survival, body weight, and motor skills were improved and neuronal damage was delayed in mice receiving the dietary supplement. Thus, creatine appears to be neuroprotective in both the traumatic injury and HD models of neurological dysfunction.

Implications: These results provide clues to the mechanisms responsible for damage following traumatic brain injury and may lead to use of creatine as a neuroprotective agent. This information may be especially important for athletes who have an increased risk of blows to the head from such full-contact sports as boxing, football, hockey, and soccer. Creatine supplementation could also be used as a palliative therapy in people at risk for developing Huntington's disease or stroke. As a dietary supplement, creatine demonstrates the potential to provide reasonably simple and effective protection from neuronal damage caused by energy imbalance.

Sullivan PG, Geiger JD, Mattson MP, and Scheff SW: Dietary supplement creatine protects against traumatic brain injury. Annals of Neurology 48: 729-729, 2001.

Ferrante RJ, Andreassen OA, Jenkins BG, Dedeoglu A, Kuemmerle S, Kubitius JK, Kaddurah-Daouk R, Hersch SM, and Beal MF: Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease. Journal of Neuroscience 20: 4389-4397, 2000.

The Brain's Dopamine Neurons Require Estrogen

Background: Men are more likely to develop Parkinson's disease (PD) than pre-menopausal women, but the reasons for this gender disparity are not fully understood. Sex hormones such as estrogen could be one factor, since the likelihood of developing Parkinson's disease increases for women after menopause. In addition, postmenopausal women with PD improve with estrogen replacement therapy. These observations suggest that estrogen might influence the survival of the dopamine-containing neurons that degenerate in PD.

Advance: Through studies in nonhuman primates, researchers have now discovered a link between estrogen and the number of dopamine neurons in the brain. Ten days after removing the ovaries, the major source of estrogen in females, investigators counted the number of dopamine neurons in the vulnerable brain region. Compared to animals that received estrogen replacement therapy, the number of dopamine neurons in estrogen-deficient female animals was reduced by about 40 percent. Estrogen replacement therapy was able to rescue these neurons following 10, but not 30, days of estrogen deficiency.

Implications: The connection between estrogen and the survival of dopamine neurons in the brain brings scientists much closer to understanding the gender and age disparities in the rate of PD in the population. Symptoms of PD begin after extensive loss of dopamine neurons, estimated at ~80 percent of the total cell number. Since estrogen protects ~40 percent of dopamine neurons from degeneration, this study identifies estrogen replacement therapy as a potential preventive measure for postmenopausal women at risk for PD. Further research into the effects of sex hormones on neuronal survival should benefit PD therapies for both men and women.

Leranth C, Roth RH, Elsworth JD, Naftolin F, Horvath TL, and Redmond DE: Estrogen is essential for maintaining nigrostriatal dopamine neurons in primates: implications for Parkinson's disease and memory. Journal of Neuroscience 20: 8604-8609, 2000.

Managing Chronic Tension-type Headache

Background: Tension headaches involve a prolonged and painful tightening of head and neck muscles. About 2-3 percent of Americans experience these headaches chronically, more than 15 days each month, nearly every day for some people. Most people use over-the-counter analgesics to treat tension headaches, but overuse can make the problem worse. Physicians have prescribed behavioral stress management techniques and drugs, but the problem can be difficult to treat. Tricyclic antidepressants are the drugs most often prescribed for the condition. Tricyclic refers to the chemical structure of the compounds. Antidepressant arises from the first use of these drugs, which have since proven useful for other problems than depression, including several chronic pain conditions. There has been conflicting evidence about the effectiveness of tricyclic drugs for chronic tension headache, and little information about the relative effectiveness of behavioral interventions alone and in combination with the drugs.

Advance: A randomized, controlled clinical trial followed two hundred adults with chronic tension-type headaches for six months. The trial evaluated two tricyclic antidepressant drugs alone or in combination with behavioral stress management. The results showed that the drugs and the behavioral therapy each improved headaches better than placebo. The drugs acted more quickly than the stress management program, but the patients who received the combination of drugs and behavioral treatment were, in the long run, most likely to show improvement.

Implications: The results of the trial provide guidance for physicians and patients coping with chronic tension-type headaches. The active treatments reduced the number of days with at least moderately severe headache from about 14 days to fewer than 7 days a month. This is clearly progress, but it highlights the need for further studies to develop therapies that are even better.

Holroyd KA, O'Donnell FJ, Stensland M, Lipchick GL, Cordingley GE, and Carlson BW: Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination. The Journal of the American Medical Association 285: 2208-2215, 2001.

Transient Ischemic Attacks Warn of a High Risk for Stroke

Background: A transient ischemic attack (TIA) is like a stroke, but the symptoms disappear quickly – most within an hour, although some may persist for a day. Estimates suggest 300,000 people experience TIAs each year in the U.S. Some experts believe the number is much higher. TIAs are often difficult to diagnose, partly because the problems may disappear before patients reach a doctor for evaluation. Many people ignore the symptoms and do not seek medical attention. Some doctors and hospitals may send patients home after diagnosing a TIA, leaving a full work-up for a week or two. No studies have thoroughly evaluated how likely it is that a serious stroke may follow a TIA and how soon that might happen.

Advance: A new study determined the risk of stroke following emergency department diagnosis of a TIA in 1707 patients. During the 90 days following a TIA, 10.5 percent of these patients experienced a stroke. The likelihood of stroke was thus increased more than 50 times in patients following a TIA compared to other people of the same age. What is more, half of these strokes occurred within two days of the TIA.

Implications: Patients and physicians should regard TIAs as a serious warning that a stroke may be imminent. Prompt diagnosis and treatment may help reduce the likelihood of strokes. Research over the last decade or more has shown several interventions, including surgery, drugs and other changes, that can reduce the likelihood of stroke in particular groups of patients. So, heeding the warning of a TIA may help many people avoid a catastrophic stroke.

Johnston SC, Gress DR, Browner WS, and Sidney S: Short-term prognosis after emergency department diagnosis of TIA. The Journal of the American Medical Association 284: 2901-2906, 2000.

A Vaccine is Highly Effective for Preventing Ebola Virus Infection in Primates

Background: Ebola virus is one of a group of viruses that causes hemorrhagic fever in monkeys and humans. It is an extremely virulent pathogen that kills up to 90 percent of infected individuals. The prevailing scientific view is that Ebola is maintained in an as yet unidentified animal species native to the African continent and is transmitted to humans through contact with that species. Of the four known strains of the Ebola virus – Zaire, Sudan, Ivory Coast, and Reston – the Zaire strain is responsible for the most human deaths. This strain of Ebola virus kills quickly, giving the body little time to develop natural immunity. No effective antiviral therapy is currently available. An effective vaccine against Ebola virus is therefore urgently needed and offers the best hope for preventing this dreaded disease.

Advance: Scientists have developed a new, DNA-based vaccine that prevents Ebola virus infection in monkeys. Unlike traditional vaccines, typically made from viral proteins, DNA vaccines more closely mimic virus infection because they enter a cell and use that cell's machinery to create new viral proteins. Researchers believe this strategy might better trick the immune system into thinking a real virus infection has occurred. To create a vaccine against multiple strains of Ebola virus, the scientists combined genes responsible for the production of surface proteins from each strain, and another virus structural protein that is common to all strains. This multi-strain DNA vaccine produced an equally powerful immune response in guinea pigs compared to a single-strain (Zaire strain) vaccine they had tested previously in these rodents. The response to the DNA vaccine was then boosted by an injection with an adenovirus vector that also makes the surface protein, but may better deliver the gene to specialized cells of the immune system. (This weakened form of adenovirus can enter cells without reproducing or causing disease). The prime-boost immunization strategy (consisting of the multi-strain DNA vaccine followed by the adenovirus booster) produced a stronger immune response than that observed with the multi-strain DNA vaccine in rodents. When this prime-boost immunization strategy was tested in monkeys, all test animals exhibited strong anti-Ebola immune responses and survived subsequent exposure to lethal doses of Ebola Zaire virus. Further, the vaccinated monkeys remained symptom-free, with no detectable virus in their blood for the duration of the study.

Implications: This first primate model of immune protection against Ebola virus may allow scientists to design a vaccine that prevents the disease in humans. Vaccination is the best hope for preventing infection and limiting the spread of Ebola virus. An effective vaccine must protect against multiple strains of Ebola virus. By studying the mechanism of protection induced by the vaccine, scientists can identify the immune system responses that protect monkeys against infection. Scientists hope to use this information to create a safe and effective vaccine and therapies against Ebola virus infection, and possibly other infectious causes of hemorrhagic fever.

Sullivan NJ, Sanchez A, Rollin PE, Yang ZY, and Nabel GJ: Development of a preventive vaccine for Ebola virus infection in primates. Nature 408: 605-609, 2000.

A Live Attenuated Dengue Virus Vaccine Candidate is Safe and Stimulates a Protective Immune Response in Human Volunteers

Background: Dengue, a mosquito-borne viral infection, has emerged as an international public health concern. The dengue virus causes two diseases – dengue fever and dengue hemorrhagic fever. Globally, there are an estimated 50 to 100 million cases of dengue fever and several hundred thousand cases of dengue hemorrhagic fever. Dengue fever can cause severe aches and pains, headaches, and high fever. Dengue hemorrhagic fever is a more serious, often fatal, illness that includes internal hemorrhaging and dramatic loss of blood pressure. Each of the four closely related types of dengue virus (Dengue virus types 1-4) causes the full spectrum of dengue disease in humans. No virus-specific treatment is available, and a vaccine is needed to reduce the burden of this disease. Although several dengue vaccine candidates consisting of live attenuated (weakened) viruses are under development, none is licensed yet. (Live attenuated virus vaccines, such as the previously used oral polio vaccine, do not normally cause disease but trigger an immune response that protects against disease-causing forms of the virus.) Recombinant DNA technology has greatly aided the development of additional promising live attenuated dengue vaccine candidates. Through this technology, scientists created a vaccine candidate, called 2A/30, which was protective for monkeys.

Advance: Scientists tested the recombinant 2A/30 vaccine, which is directed against dengue virus type 4, in 20 human volunteers. They found that the vaccine is well tolerated, safe, and generates an immune response against type 4 dengue virus. It produced few clinical symptoms in vaccine recipients, none of which interfered with daily activities or required treatment. The researchers also showed that the attenuated 2A/30 virus is not readily transmitted to mosquitoes, and thus is not likely to be passed in a mutated, disease-causing form from mosquitoes to unvaccinated individuals. The 2A/30 virus grows well in cultured monkey cells, which could be used to manufacture the vaccine in the laboratory.

Implications: The results indicate the feasibility of using modern molecular techniques to create dengue virus vaccines that could prevent the millions of dengue cases that occur annually worldwide. The vaccine candidate 2A/30 not only shows promise as a vaccine against type 4 dengue virus, but serves as a basis for creating a vaccine that protects against all four types of dengue virus. The high degree of immune response and very mild symptoms generated by this vaccine are encouraging. Researchers have already planned further evaluation of this vaccine candidate in larger, controlled studies in humans.

Durbin AP, Karron RA, Sun W, Vaughn DW, Reynolds MJ, Perreault JR, Thumar B, Men R, Lai CJ, Elkins WR, Chanock RM, Murphy BR, and Whitehead SS: Attenuation and immunogenicity in humans of a live dengue virus type 4 vaccine candidate with a 30 nucleotide deletion in its 3'-untranslated region. American Journal of Tropical Medicine and Hygiene 65, (in press 2001).

Troyer JM, Hanley KA, Whitehead SS, Strickman D, Karron RA, Durbin AP, and Murphy BR: A live attenuated recombinant dengue-4 virus vaccine candidate with restricted capacity for dissemination in mosquitoes and lack of transmission from vaccinees to mosquitoes. American Journal of Tropical Medicine and Hygiene 65, (in press 2001).

Use of Umbilical Cord Blood as a Source of Stem Cells for Transplantation

Background: Bone marrow is the spongy tissue inside bones that produces hematopoietic (blood-forming) stem cells (HSCs), which grow and divide to produce the body's blood cells, including immune system cells. Bone marrow transplantation is commonly used to treat diseases that cause the marrow to produce either abnormal blood cells or greatly reduced numbers of normal blood cells. These diseases include certain types of cancer, such as leukemia and lymphoma, as well as noncancerous diseases, such as aplastic anemia and thalassemia. In bone marrow transplantation, doctors destroy the bone marrow of the recipient using drugs and radiation and replace it with healthy transplanted marrow, which produces new, healthy blood cells. A potentially life-threatening complication of bone marrow transplantation is graft-versus-host disease (GVHD), in which immune cells in the transplanted bone marrow (the "graft") attack the tissues of the patient who received the transplant (the "host"). An alternative to transplanting bone marrow is to transplant umbilical cord blood, which also contains HSCs, and is easier and cheaper to obtain. Research has suggested that the risk of GVHD might be lower with cord-blood transplants than with bone marrow transplants because the immune cells that cause GVHD are immature in cord blood and therefore less likely to produce unwanted immune responses. This theory, however, needed to be tested with a large number of patients using a statistical method that adjusts for other factors known to influence the risk of GVHD.

Advance: Investigators determined that pediatric recipients of cord-blood transplants had a significantly lower incidence of both acute and chronic GVHD than pediatric recipients of bone marrow transplants, although death rates in the two groups were comparable. The researchers evaluated the effectiveness of the two approaches by comparing the records of 113 children who received cord-blood transplants and 2,052 children who received bone marrow transplants. In both groups, the transplants were taken from siblings who were genetically similar to minimize the risks of transplant rejection and GVHD.

Implications: These findings indicate that cord blood is as effective as bone marrow as a source of HSCs for children who receive transplants from genetically matched siblings. In addition, cord-blood transplants are far less likely than bone marrow transplants to cause GVHD. Because few patients are able to obtain cord blood from genetically similar siblings, this study should be replicated with recipients of genetically matched cord blood and bone marrow from unrelated donors.

Rocha V, Wagner JE, Sobocinski KA, Klein JP, Zhang MJ, Horowitz MM, and Gluckman E: Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. The New England Journal of Medicine 342: 1846-1854, 2000.

Public Service Announcements Geared to Address Teens' Specific Motivation to Use Drugs Can Reduce Drug Use

Background: Researchers have gained greater insight into why people use drugs. For example, we now know there are at least two major categories of drug users. One group includes people who are simply novelty seekers, using drugs solely for their sensational effects. The second group is using drugs as if they are anti-anxiety or anti-depressant substances, trying to compensate for untreated mental disorders like depression or for terrible living situations, such as dysfunctional families. The prevention and treatment approaches directed at each group differ significantly. Prevention messages must be developed that target the individual's motivation to use drugs. Researchers who were interested in reducing marijuana use among a group of adolescents identified as high sensation seekers, found some promising results when they developed targeted public service announcements (PSAs) specifically tailored to these youth.

Advance: Researchers recently reported that they could reduce marijuana use among a targeted group of teens by focusing on their specific underlying emotional styles. By developing anti-marijuana PSAs that appeal to high sensation seeking adolescents and placing them in programs likely watched by these teens, the researchers found that marijuana use among this group was reduced by about 26 percent. Sensation seeking is a personality trait associated with the willingness to take risks to obtain intense stimulation and has been shown to be correlated with the use of a variety of drugs and use at an earlier age. An average of 777 paid spots and 1,160 unpaid spots were aired in 3 similar communities in Kentucky and Tennessee. At least 70 percent of the targeted age group was exposed to a minimum of three PSAs a week. The campaigns were successful in reversing the usual trend of more teens beginning to use marijuana as they get older. In one community, effects of the campaign still were evident several months after its conclusion. There, the estimated drop in the relative proportion of high sensation seekers using marijuana was 26.7 percent. The campaigns had no effect on teens characterized as low sensation seekers, a group that already exhibited low levels of marijuana use.

Implications: Although research generally has shown that media campaigns coupled with other kinds of interventions are the most successful, this study shows that media campaigns alone can have significant reductions in high risk adolescents' marijuana use. Further, the effects can be long lasting. However, these results appear to be specific to the substance targeted as the researchers found no effects on tobacco, alcohol, inhalant, cocaine, or hallucinogen use. Nonetheless, carefully targeted campaigns with sufficient exposure can play an important role in drug abuse prevention efforts.

Palmgreen P, Donohew L, Lorch EP, Hoyle RH, and Stephenson MT: Television campaigns and adolescent marijuana use: tests of sensation seeking targeting. American Journal of Public Health 91: 292-296, 2001.

Advances in Development of an AIDS Vaccine

Background: One of the major challenges to gain control of the worldwide AIDS epidemic is the need to develop an effective vaccine. The retrovirus that causes an AIDS-like condition in macaque monkeys is an important tool in understanding the factors that are important for disease induction and progression both in monkeys and humans.

Advance: Scientists at the Vaccine Research Center and Yerkes Regional Primate Research Center at Emory University, collaborating with researchers at other institutions, have developed a vaccine that stimulates an immune response against several viral proteins. Macaque monkeys were immunized twice with DNA encoding a number of simian immunodeficiency virus (SIV) and human immunodeficiency virus (HIV-1) proteins, which stimulated an initial immune response. Twenty-four weeks after the initial immunization, the animals received a booster shot with an animal poxvirus that does not replicate in human or animal cells. As the DNA used in the first immunization, this virus was engineered to encode a variety of SIV and HIV proteins. The immunizations proved highly effective. Seven months after the booster immunization, the investigators administered intrarectally a high dose of an extremely pathogenic virus containing both SIV and HIV genes (therefore known as SHIV). Although the immunizations did not prevent virus infection, the vaccinated animals only had low levels of SHIV in their blood and did not become ill. In contrast, three of four nonvaccinated control animals had died of AIDS by 23 weeks after virus administration.

Implications: This vaccine combination was shown to control a highly pathogenic immunodeficiency virus in the rhesus monkey and demonstrates the extremely important potential for providing a relatively simple vaccine to help control AIDS in humans.

Amara RR, Villinger F, Altman JD, Lydy SL, O'Neil SP, Staprans SI, Montefiori DC, Xu Y, Herndon JG, Wyatt LS, Candido MA, Kozyr NL, Earl PL, Smith JM, Ma HL, Grimm BD, Hulsey ML, Miller J, McClure HM, McNicholl JM, Moss B, and Robinson HL: Control of mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine. Science 292: 69-74, 2001.

Steroid-free Immunosuppression for Kidney Transplantation in Children

Background: Corticosteroids, which belong to a family of compounds that form the backbones of several hormones and cholesterol, are normally produced by the outer layer of the suprarenal glands called the adrenal cortex. Corticosteroids affect a variety of essential metabolic processes and have been a cornerstone of immunosuppressive therapy for 40 years despite a host of adverse side effects. In the past, attempts to reduce or stop administration of steroids from pediatric recipients of kidney transplants have commonly ended in organ rejection.

Advance: To test if a complete steroid-free drug regimen with new, advanced immunosuppressive drugs would be able to prevent rejection of transplanted kidneys, investigators at the Stanford University General Clinical Research Center developed a regimen consisting of three non-steroidal drugs to suppress the immune system of 10 children, 5 to 21 years old, through their pre- and post-transplant periods. These agents, daclizumab, tacrolimus, and mycophenolate mofetil, resulted in a 100 percent survival rate for both graft and patients. Furthermore, side effects such as high blood pressure, high cholesterol, and facial and body disfigurement, commonly seen in patients who are immunosuppressed by steroids, were not observed with this new treatment. Although it began only 14 months ago, this approach holds great promise for all transplant recipients.

Implications: Complete steroid-free immunosuppression works well and is safe in this selected group of children. Furthermore, the protocol avoids the morbid side effects of steroids, does not increase infection rates, and optimizes kidney function and childhood growth.

Sarwal MM, Yorgin PD, Alexander S, Millan MT, Belson A, Belanger N, Granucci L, Major C, Costaglio C, Sanchez J, Orlandi P, and Salvatierra O Jr.: Promising early outcomes with a novel, complete steroid avoidance immunosuppression protocol in pediatric renal transplantation. Transplantation 72: 13-21, 2001.

Maternal Antibody Can Protect Newborns Against Diseases Like Meningitis, Pneumonia, and Blood Stream Infections

Background: Group B streptococcus (GBS) is a major cause of early-onset diseases such as meningitis, pneumonia, and blood stream infections in newborns. Vaccine-induced antibodies protect against GBS in mice. Testing the experimental GBS vaccines in humans, however, will require large sample sizes since the incidence of disease has been significantly reduced as an increasing number of women are given antibiotics during childbirth. If an experimental vaccine were given to women before or during pregnancy, it would take a large number of women and a great deal of time to test its efficacy in preventing disease. Thus, to avoid these problems, NIH scientists proposed that licensure be granted to GBS vaccines that can be shown to induce protective levels of antibodies that are specific to GBS. This would eliminate the need for separate and costly efficacy trials. To simplify this challenge, scientists conducted a study that examined the relationship between the level of antibodies in mothers and the presence of any diseases caused by GBS in newborns.

Advance: The scientists first collected serum samples from mothers and their newborns during labor and delivery, before the infants showed any signs of disease. Next, the scientists compared the antibody levels between mothers whose infants had a GBS disease to those who did not. The scientists found that the probability of having a disease caused by GBS in newborns declined with increasing antibody levels in the mothers. Specifically, mothers with at least 5 micrograms of antibodies per milliliter of serum had an 88 percent lower risk of having an infant who developed a disease such as meningitis, pneumonia, and blood stream infections compared to mothers with less than 0.5 micrograms of antibodies per milliliter.

Implications: Based on this innovative study, scientists can now predict that vaccines that induce protective antibody levels that reach at least 5 micrograms per milliliter in the mother, can confer a high degree of immunity against such diseases caused by GBS in the newborn. More importantly, the findings will help to simplify and speed the licensure of a GBS vaccine to help prevent serious newborn diseases much more quickly than if scientists were required to conduct efficacy trials.

Lin FY, Philips JB III, Azimi PH, Weisman LE, Clark P, Rhoads GG, Regan J, Concepcion NF, Frasch CE, Troendle J, Brenner RA, Gray BM, Bhushan R, Fitzgerald G, Moyer P, and Clemens JD: Level of maternal antibody required to protect neonates against early-onset disease caused by type 1a group B streptococcus: a multi-center, seroepidemiology study. Journal of Infectious Diseases (in press 2001).

HIV Prevention Program Helps Reduce Sexual Activity Among Minority Youth

Background: Previous research has demonstrated that individuals who feel connected to their communities are less likely to engage in behaviors that are damaging to their communities and to themselves. NIH-supported scientists put these findings to practical use by developing an innovative strategy to reduce the persistently high rates of pregnancy and sexually transmitted diseases (STDs), as well as the growing rate of HIV infection, among teens. The researchers designed a “service learning” intervention program, called “Reach for Health.” This intervention combined comprehensive health education with activities that allowed teens to serve their community by working in such organizations as day care centers and nursing homes. A total of 195 African-American and Hispanic students completed the study, which started in the fall of grade 7 and ended with completing surveys in the spring of grade 10. Researchers evaluated how effective the program was in delaying the teen’s first sexual intercourse, and in reducing pregnancies and frequency of sex.

Advance: The findings revealed that students who were involved in the service learning program were significantly less likely to begin or to be involved in any recent sexual activity than students who participated only in the health education program. Previous research showed that the effects of similar types of service learning programs lasted for only short periods of time. However, this study is the first to document that a service learning program could influence student behavior for as long as two years after the youth were involved in the program. Furthermore, the program produced significant differences in the proportion of youth engaging in high risk behavior. For example, the proportion of males who began having sexual intercourse between grades 7 and 10 was 80 percent among those who received health education only, 62 percent among those who participated in the service learning program for one year, and only 50 percent among those who participated in the program for two years. In addition, the proportion of females who reported ever being pregnant was 18.5 percent among those who received health education only, compared with 10.3 percent among those who participated in the service learning program for one year, and 6.8 percent among those who participated in the program for two years.

Implications: These results provide strong evidence that creative, research-based interventions, delivered to youth in their early teens, can delay sexual activity during a critically important developmental stage. Furthermore, the positive impact of such programs can last for a significant and critical period of time. In addition, the findings reinforce previous evidence that curriculum-only interventions are not enough to reduce risky behaviors in the long term, especially among the most vulnerable youth. Researchers believe that this program is successful because it requires students to reflect on the meaning of the service they perform, both from a personal and community perspective, while connecting it directly to what they learn in school. In demonstrating the effectiveness of such a program, the researchers have also expanded the range of prevention programs that can better meet school and community needs. Finally, the research is timely, as it coincides with the increasing popularity of community service programs being adopted by school districts around the Nation.

O’Donnell L, Stueve A, O’Donnell C, Duran R, San Doval A, Wilson RF, Haber D, Perry E, and Pleck JH: Long-term reduction in sexual initiation and sexual activity among urban middle school participants in the Reach for Health Community Youth Service Learning HIV Prevention Program. Journal of Adolescent Health (in press 2001).

Virginity Pledges Help Some Adolescents Delay Sexual Activity

Background: For many years, researchers have documented that early sexual intercourse increases the risk of unwanted pregnancy and sexually transmitted diseases (STDs). As a result, many researchers have designed and tested interventions to prevent or delay early sexual activity. Most of this research has focused on comprehensive strategies that combine safer-sex messages with abstinence messages. Few researchers, however, have evaluated strategies that promote *abstinence-only* messages. As a result, little is known about whether abstinence-only messages actually delay sexual activity, and under what circumstances they are most effective. During the 1990s, a variety of religious and community groups began to encourage teenagers and young adults to take pledges to remain virgins until they marry. As of 1995, more than two and a half million teens had made such pledges, either publicly or in writing. To better understand the impact of abstinence-only messages, NIH investigators studied the effects of these virginity pledges on teenage sexual activity. The researchers conducted their analysis using data from the National Longitudinal Study of Adolescent Health, a comprehensive survey of 90,000 seventh-through-twelfth graders.

Advance: After accounting for a wide range of pre-existing differences that distinguished teens who made virginity pledges from those who did not, researchers found that pledgers delayed having sexual intercourse about one-third longer than their peers who did not take such a pledge. However, the effectiveness of taking a pledge depended on the students' age: pledging had no effect on older teens, ages 18 and over, but among 16 and 17 year olds, taking a pledge had a strong and consistent impact on whether they delayed sex. Among the youngest teens, ages 12-15, pledging delayed sex only if the adolescents were part of a supportive group of other adolescents who were making the same commitment, and only if pledging was rare enough in the adolescent's larger social world to set the group of pledgers apart from other teens. The study also found that among those adolescents who eventually did initiate sexual intercourse, pledgers were no more likely than non-pledgers to suffer losses in self esteem. This is an important finding since critics of the pledge have argued that those who break their pledge to initiate sexual activity will feel guilty and lose self esteem. One of the study's most significant findings, however, was that adolescents who had taken the pledge were less likely to use contraception at their first sexual experience than those who had not, placing them at a greater risk for an unwanted pregnancy or STDs such as HIV/AIDS.

Implications: These results indicate that virginity pledges can be effective in helping *some* teens to delay sexual intercourse, but will not work for all teens. In addition, these results provide sound and substantial information about the circumstances under which the pledge is effective. This information can help educators and others who work with youth plan interventions to help adolescents avoid early sexual activity and its consequences. Ultimately, such efforts can contribute to this country's larger goal of reducing the rates of STDs and unplanned parenthood in teenagers.

Bearman PS, and Brückner H: Promising the future: virginity pledges and first intercourse. American Journal of Sociology 106: 859-912, 2001.

Early Childhood Program Reduces Crime and Dropout Rates

Background: According to the National Center for Education Statistics, by 1995 nearly 13 million children were in child care. Since these programs vary in quality and types of activities, it is important to evaluate which ones get children off to a good start in life. One such program, the Chicago Child-Parent Center, began in 1967, making it the second oldest federally funded early childhood intervention program in the country. The program's 23 centers provide poor, inner city children in the Chicago public school system with comprehensive early education from ages three to nine. The programs emphasize language and literacy development and offer family support services to promote children's school readiness and healthy social functioning into adolescence and adulthood. As part of an ongoing longitudinal study, NIH-supported researchers are following a sample of over 1,200 minority children who attended this program and are now young adults. The researchers are interested in whether the children cope effectively with everyday responsibilities in school and in life. In addition, researchers are assessing which components of early childhood programs improve outcomes for children in inner-city, high-poverty neighborhoods, and the duration, intensity, and costs of services required for developing the skills children need to succeed.

Advance: Researchers found that this Chicago early intervention program created positive effects that could be observed 15 years later when the children reached adolescence and moved into adulthood. In particular, children who were in the program for at least one or two years were less likely to commit crimes as teens or to drop out of high school, compared to children in similar family and economic circumstances who attended other public pre-kindergarten programs or who did not attend a program. Children who began the program at preschool-age had the lowest dropout and crime rates 15 years later. High school graduation rates were 30 percent higher for children who had spent one or two years in the program as preschoolers. In addition, children who had attended the program had juvenile arrest rates that were 33 percent lower and violent crime rates that were 41 percent lower than the other children. Researchers also showed that every dollar spent on the program returned four dollars to society by reducing public spending on remedial education and other corrective programs.

Implications: This is a unique and unparalleled long-term evaluation of an early childhood program. In addition to being the only study of a publicly funded school program serving the poorest inner city children, it includes ten times more children than similar studies of such programs and has retained most of the initial study participants. Furthermore, the research design includes appropriate comparison groups that are absent in other evaluation research. This study is also useful for policymakers who must establish funding priorities, since it provides a detailed analysis of program costs relative to benefits for both participants and society. The next phase of the research will answer a set of complex and typically neglected questions, such as which specific parts of the program work for particular children, but not others, and exactly how the program produces a positive influence on behavior. These results will help researchers develop even more effective early childhood programs.

Reynolds AJ, Temple JA, Robertson DL, and Mann EA: Long-term effects of an early childhood intervention on educational achievement and juvenile arrest. The Journal of the American Medical Association 285: 2339-2346, 2001.

A Potential DNA Vaccine for AIDS

Background: The search for an AIDS vaccine has been one of the most intense yet frustrating quests of modern medicine. Most scientists agree that prevention is critical to control HIV infection, and numerous laboratories have taken various approaches to devise an effective vaccine. Despite identification of HIV more than 15 years ago, the efforts to come up with a vaccine have been confounded by the diversity of the virus and the difficulty identifying antigens that produce long-lasting immunity. Some of the most promising work has occurred in studies with monkeys; during the past 10 years, Dr. Norman Letvin, Harvard Medical School, has investigated control of simian immunodeficiency virus (SIV) infection in rhesus monkeys. These monkeys develop simian AIDS within 6 months of infection, making them an excellent animal model in which to investigate possible vaccine strategies. Letvin has looked specifically at responses of cytotoxic T lymphocytes (CTL), which recognize and kill cells displaying foreign antigens. In human studies, potent CTL responses have been correlated with keeping HIV from replicating, maintaining a low virus load, and a stable clinical status, suggesting that an effective HIV vaccine should stimulate HIV-specific CTLs.

Advance: Test monkeys were vaccinated with a DNA vaccine augmented by interleukin-2 proteins, which enhance immune response; control animals were treated with a vaccine that was not augmented. All animals were then given a large intravenous dose of SIV. All of the monkeys became infected, but there was neither virus replication nor disease progression in those treated with the augmented vaccine. Monkeys in the control group rapidly lost immune function and exhibited significant clinical signs of disease; half were dead within 140 days of infection. In contrast, monkeys who received the augmented vaccine demonstrated stable immune systems, low or undetectable viral loads, and no evidence of clinical disease or mortality within 140 days of infection.

Implications: This work demonstrates for the first time that an SIV vaccine can prevent overt simian AIDS, a significant step forward in the battle against AIDS. The results raise the possibility that a similar vaccination for humans might reduce replication of HIV in people who have been vaccinated and then subsequently infected with HIV. Vaccinated individuals might have decreased viral burdens and lower rates of HIV transmission, which may assist in the control of AIDS and AIDS-associated malignancies.

Barouch DH, Santra S, Schmitz JE, Kuroda MJ, Fu TM, Wagner W, Bilska M, Craiu A, Zheng XX, Krivulka GR, Beaudry K, Lifton MA, Nickerson CE, Trigona WL, Punt K, Freed DC, Guan L, Dubey S, Casimiro D, Simon A, Davies ME, Chastain M, Strom TB, Gelman RS, Montefiori DC, Lewis MG, Emini EA, Shiver JW, and Letvin NL: Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented DNA vaccination. Science 290: 486-492, 2000.

Nabel GJ: Challenges and opportunities for development of an AIDS vaccine. Nature 410: 1002-1007, 2001.

Weiss, R: AIDS: unbeatable 20 years on. The Lancet 357: 2073-2074, 2001.

Study Documents Strong Association Between Cigarette Promotion and Initiation of Smoking in Adolescents

Background: The relationship between the marketing of tobacco products and adolescent smoking has long been controversial. The tobacco industry maintains that it has no intention to advertise and promote cigarettes to young people. In developed countries such as the U.S., the industry claims that its marketing is aimed exclusively at persuading current smokers to switch brands. Yet it is clear that a dynamic market exists for tobacco products. Every day some tobacco users die or quit smoking, and they are replaced by new smokers, most of whom are adolescents. In the past, researchers have had difficulty measuring exposure to cigarette marketing in population-based studies of adolescents. The introduction of cigarette promotional items – clothing and other products bearing cigarette brand logos – has made it possible to quantify exposure to such marketing, and several studies have shown that ownership of cigarette promotional items correlates with higher levels of smoking uptake. Information has been lacking, however, on two key issues: how receptivity to cigarette promotions changes over time, and how changes affect smoking behavior.

Advance: In a study of 480 students in grades 4 to 11, NIH-supported researchers have shown that, over time, the likelihood that an adolescent will start smoking increases when he or she acquires a cigarette promotional item or becomes willing to use one. Conversely, the likelihood that an adolescent will start smoking declines when he or she loses a cigarette promotional item or becomes unwilling to use it. The study is the first to survey students' smoking behavior and attitudes to cigarette promotions at three points in time; previous studies had looked at no more than two points in time. Initiation of smoking was significantly higher among students who in the first survey were receptive to cigarette promotions (that is, they owned a cigarette promotional item or were willing to use one). Smoking initiation was also higher among students who were not receptive to cigarette promotions in the first survey but became so by the second or third survey. Students who were initially receptive to cigarette promotions but became non-receptive in later surveys were less likely to become smokers. In summary, the study documents a strong and statistically significant association between receptivity to cigarette promotions and increased smoking uptake over time in a cohort of adolescents.

Implications: The study results support a close linkage between tobacco promotional activities and adolescent smoking. They support the concept that exposure to tobacco marketing influences adolescents' attitudes and beliefs, which in turn prompts smoking initiation, and also helps to shape the self-identity of the experimental smoker into that of a smoker. These results strengthen the evidence about the harmful effects of cigarette promotions and suggest that elimination of cigarette promotional campaigns could reduce adolescent smoking.

Sargent JD, Dalton M, Beach M, Bernhardt A, Heatherton T, and Stevens M: Effect of cigarette promotions on smoking uptake among adolescents. Preventive Medicine 30(4): 320-327, 2000.

Rebelliousness and Risk-taking in Fifth Graders Predict Cigarette Smoking by Twelfth Grade

Background: Cigarette smoking is implicated in many diseases. Most smokers start fairly young, and evidence indicates that even high school seniors are already trying to stop. Clearly prevention is important. Developing an effective smoking prevention program would require understanding why young people start to smoke in the first place. Asking people for information on past behavior can skew the results with biased memory, and people may filter their ideas of their earlier motivations in the light of later experiences. A “prospective” study, one that chooses a group of subjects and then investigates what happens to them over time, eliminates the memory and filter biases. Such a study is best for gathering the personality and motivation information that scientists need for effective smoking prevention.

Advance: In one of the largest prospective studies to examine smoking and personality, researchers found that the tendency to rebelliousness and risk-taking in fifth grade youngsters correlated the most with later smoking. The scientists evaluated the extent to which personality variables in 3,130 fifth graders would predict smoking at 12th grade. Scientists tested the children for a propensity toward rebelliousness, risk-taking, helplessness in the face of problems, their ability to regulate their facial expressions and body language (termed their “affect”), early maturation, and susceptibility to peer compliance and peer approval. Seven years later, scientists were able to predict the smoking habits for almost all of the students. The most significant predictors of smoking were rebelliousness and a tendency to risk-taking. The other measures did not significantly predict smoking, including whether the youngster was a boy or a girl, nor their history of early smoking. Contrary to commonly held belief, their susceptibility to peer influence also did not predict smoking.

Implications: Some personality characteristics may predispose young people to smoking; knowing what these characteristics are may be effective in identifying high risk groups. In any case, smoking prevention programs for young people should start before fifth grade and be designed to incorporate the needs and expectations of rebellious and risk-taking youth.

Burt RD, Dinh KT, Peterson AV and Sarason IG: Predicting adolescent smoking: a prospective study of personality variables. Preventive Medicine 30(2): 115-125, 2000.

Burt RD, and Peterson AV: Smoking cessation among high school seniors. Preventive Medicine 27(3): 319-327, 1998.

Relatives of People with Pancreatic Cancer are Probably at Increased Risk of the Cancer

Background: Pancreatic cancer tends to cluster in some families, which suggests an inherited basis for the disease in some cases. However, cancer may also occasionally cluster in a family because of a shared environment where family members may smoke or may work in an industry with toxic chemicals, so the presence of such a cluster does not in and of itself prove that the disease is inherited. Recent studies have compared the history of people with pancreatic cancer with the tendency of their relatives to contract the disease, and the results have indicated pancreatic cancer clusters are much more likely to be due to genetics than to environmental influences. The study conclusions are less than firm, though, because those were “retrospective” studies, that is, ones that look into the past. They suffer from inherent biases of skewed memory and reporting. A “prospective” study, in which the scientists choose the subjects and then track what happens to them after that date, was needed.

Advance: For the first time, scientists prospectively followed the relatives of pancreatic cancer patients to establish their risk of getting cancer. Scientists examined patients and their families entered in the National Familial Pancreas Tumor Registry (NFPTR) at the Johns Hopkins Hospital. They separated the pancreatic cancer patients into two groups. Those having two close relatives with pancreatic cancer fell into one of the 244 “Familial Pancreatic Cancer kindreds.” Those with at least one family member with pancreatic cancer, but not two close relatives, were assigned to the 291 “Sporadic Pancreatic Cancer kindreds.” Researchers found that close relatives in the Familial Pancreatic Cancer kindreds developed pancreatic cancer at a rate tens of times higher than the general population. Sporadic Pancreatic Cancer kindreds also developed the disease at a lesser but still significantly higher rate. Smoking contributed to increased rates in both types of kindreds, but evidence indicated that it did not fully explain the higher incidence.

Implications: This study’s results suggest that in some families, pancreatic cancer may be an inherited disease. In fact, although there are other clusters of genetically-derived cancers, this familial pancreatic cancer appears to be distinct. This understanding is a step forward in understanding the nature of this cancer, its treatment, and its prevention. With this new information about high risk categories, it will be feasible to effectively target counselling. High risk people would also benefit from smoking cessation programs and other programs to identify and treat patients with precancerous conditions and a family history of pancreatic cancer.

Tersmette AC, Petersen GM, Offerhaus GJ, Falatko FC, Brune KA, Rozenblum E, Wilentz RE, Yeo CJ, Cameron JL, Kern SE, and Hruban RH: Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. Clinical Cancer Research 7(3): 738-744, 2001.

Obesity and Hypertension Increase Risk of Kidney Cancer Among Men

Background: Renal (kidney) cancers account for two to three percent of new cases of cancer in the U.S.. In more than 80 percent of cases, renal cancer arises from tissue within the kidney called the parenchyma. The incidence of this type of renal cancer, called renal-cell carcinoma, is one of the most rapidly increasing of all types of tumors in the U.S., particularly among African-Americans. Prior research has shown that obesity increases the risk of renal-cell carcinoma, although this association has not been consistently observed among men. Hypertension (high blood pressure) is also a risk factor, but data on this association have been limited.

Advance: To clarify the association of obesity and hypertension with renal-cell cancer, NIH researchers studied the health records of a large cohort of male Swedish construction workers diagnosed with kidney cancer. The height, weight, and blood pressure of the men had been obtained at an initial examination. Height and weight measurements were used to calculate the men's body mass indices (BMIs), which were then divided into eight sequentially increasing categories containing approximately equal numbers of patients. The investigators found that men in the middle three BMI categories had a 30-60 percent greater risk for renal-cell cancer than men in the lowest three categories. The risk among men in the highest two BMI categories was nearly double the risk of those in the lowest three categories. After excluding the first 5 years of follow-up from the analysis to reduce the possible effects of preclinical disease on the patients' risk for renal-cell cancer, the researchers found that this risk remained consistently higher in men with higher BMIs or blood pressures. At a 6-year follow-up, this risk rose higher with increasing blood pressures and decreased with lower blood pressures.

Implications: These findings suggest that men with higher body mass index and higher blood pressure have an increased long-term risk of renal-cell cancer. Effective control of weight and hypertension may be useful in the prevention of renal-cell carcinoma, an increasingly common type of cancer.

Chow WH, Gridley G, Fraumeni JF Jr, and Järnholm B: Obesity, hypertension, and the risk of kidney cancer in men. The New England Journal of Medicine 343: 1305-1311, 2000.

Association of Cancer with AIDS-Related Immunosuppression in Adults

Background: Persons infected with the human immunodeficiency virus (HIV) often have a weakened immune system, as do those with AIDS. A suppressed immune system places HIV-infected individuals at increased risk for three specific AIDS-defining cancers: Kaposi's sarcoma (KS), which affects the skin and can affect the lungs; non-Hodgkin's lymphoma; and invasive cervical cancer. Other cancers also appear to occur disproportionately in HIV-infected persons in industrialized parts of the world. However, the incidence of these non-AIDS-defining cancers varies by geographic region and HIV exposure group. This large-scale study examined the general cancer patterns among 302,834 U.S. adults with HIV/AIDS from 11 different geographical regions of the country. The study also sought to distinguish cancers associated with immunosuppression from other cancers occurring in excess among persons with HIV/AIDS (PWAs). Data from persons with HIV/AIDS were compared with cancer incidence rates in populations without HIV/AIDS.

Advance: As expected, PWAs had an excess of AIDS-defining cancers. The HIV/AIDS population studied also had elevated rates of several non-AIDS-defining cancers. However, only Hodgkin's lymphoma, lung cancer, penile cancer, soft tissue malignancies, and testicular seminoma (a type of testicular cancer) met the three criteria set by the study authors for a potential association with immunosuppression. An increased risk for Hodgkin's disease was observed as HIV infection progressed to clinical AIDS. Lifestyle factors such as heavy smoking and frequent exposure to human papillomavirus may have contributed to the increased proportions of lung cancer and penile cancer, respectively, in this study. Inaccurately recorded cases of KS may have produced the excess numbers of soft tissue malignancies found among PWAs. Thus, Hodgkin's disease and possibly lip cancer and testicular seminoma may be genuinely associated with an impaired immune system.

Implications: This large-scale analysis is the first population-based study with sufficient statistical power to examine cancer risk among PWAs by sex, race, and HIV risk group. The analysis confirms previous findings of increased risks for several non-AIDS-defining cancers (i.e., multiple myeloma, anal cancer, brain cancer, conjunctival carcinoma) in PWAs. Drawing from a substantial sample size and database of information on the test population, the current analysis, in contrast with smaller studies, can more confidently suggest that these cancers are not influenced by immune status or by the progression of HIV infection to AIDS. The non-AIDS-defining cancer most likely to be truly linked to suppressed immune function is Hodgkin's disease. The findings of this study potentially bear on treatment of PWAs. Therapies that hasten the progression of HIV infection to clinical AIDS or that accelerate the decline in immune function also may increase the likelihood of the development of certain cancers.

Frisch M, Biggar RJ, Engels EA, and Goedert JJ for the AIDS-Cancer Match Registry Study Group: Association of cancer with AIDS-related immunosuppression in adults. The Journal of the American Medical Association 285: 1736-1745, 2001.

Smokeless Tobacco Use as a Gateway for Smoking Initiation

Background: The use of smokeless tobacco, i.e., the consumption of snuff and/or chewing tobacco, is increasing in the U.S. In recent years, use has increased 32 percent among high school students and nearly 10 percent report having used smokeless tobacco. The greatest use is among rural white males. It is also common among young athletes; one study found that more than one-fifth of college athletes used smokeless tobacco. Many ill-informed users view the practice as a safe alternative to cigarette smoking. However, smokeless tobacco is associated with several serious illnesses including gum disease, nicotine addiction, cardiovascular disease, and mouth and throat cancers. It is also linked to other risky health behaviors such as binge drinking, consumption of high fat foods, and not using seat belts when driving.

Advance: It has been suggested that smokeless tobacco acts as a gateway drug to cigarette smoking, but evidence is scanty and mixed. This study, the first prospective look at the relationship, followed nearly 8,000 U.S. Air Force recruits for one year. All reported never smoking cigarettes. These young adult males are considered at high risk for any type of tobacco use. After a year, men who used smokeless tobacco (either currently or at any time in the past) were more than twice as likely as recruits who had never used smokeless tobacco to begin cigarette smoking.

Implications: The gateway role of smokeless tobacco products is an important new finding. This strong evidence of smokeless tobacco use as a significant predictor of smoking initiation among young adult males has implications for smoking prevention and cessation programs. In light of this new evidence, these programs should include strategies to prevent smokeless tobacco use or to help users quit.

Haddock CK, Weg MV, DeBon M, Klesges RC, Talcott GW, Lando H, and Peterson A: Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males. Preventive Medicine 32(3): 262-267, 2001.

Burak LJ: Smokeless tobacco education for college athletes. Journal of Physical Education, Recreation & Dance 72(1): 37-38, 2001.

Association Between Human Papillomavirus and a Subset of Head and Neck Cancers

Background: Most cases of head and neck squamous cell carcinoma can be attributed to tobacco use and alcohol consumption. However, 15-20 percent of cases occur in nonsmokers and nondrinkers, suggesting that there are other risk factors. The possible role of human papillomavirus (HPV) in the etiology of these cancers has been the subject of considerable debate. Certain HPVs (i.e., HPV16 and HPV18) are known to cause tumors in human epithelial tissues, but their role in the development of head and neck cancer has remained unclear.

Advance: NIH-funded investigators have now provided strong molecular evidence that papillomavirus is associated with a subset of head and neck cancers. In a recent study, the scientists examined tumor tissue from 253 patients with head and neck cancer, and found HPV in the tumors of 25 percent of the patients. The patients with HPV-positive tumors were less likely than other patients to be smokers or moderate-to-heavy drinkers, and their tumors were primarily oropharyngeal. The study also found that HPV-positive tumors were associated with longer survival than HPV-negative tumors.

Implications: This study offers further evidence of a causal relationship between HPV and a subset of head and neck cancers. The data suggest that HPV- positive oropharyngeal carcinomas may constitute a distinct class of cancers that have a more favorable prognosis than HPV- negative carcinomas.

Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, Zahurak ML, Daniel RW, Viglione M, Symer DE, Shah KV, and Sidransky D: Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. Journal of the National Cancer Institute 92: 709-720, 2000.

A Protein Associated with Atherosclerosis May Give New Insights into Glaucoma

Background: Primary open angle glaucoma is a major public health problem and the number one cause of blindness in African-Americans. Approximately three million Americans have glaucoma, and as many as 120,000 are now blind from this disease. Even though glaucoma was first described over 100 years ago, its pathogenesis remains elusive. Glaucoma is most commonly associated with elevated intraocular pressure; however, the precise cause of this increase in pressure in the eye is not known. Considerable evidence points to a blockage at the site from which fluid flows out of the eye as the cause of pressure elevation. The tissue that regulates the exit of fluid from the eye, the trabecular meshwork, is composed of endothelial cells (specialized cells that line blood vessels and other tissues) and noncellular components. By characterizing this specialized tissue at the cell and molecular level, scientists hope to elucidate the underlying pathology of glaucoma.

Advance: Scientists have identified a molecular marker of glaucoma in the trabecular meshwork endothelial cells. The marker, ELAM-1 (endothelial leukocyte-adhesion molecule-1), is also the earliest marker for the build up of fatty deposits, known as atherosclerotic plaques, in the linings of blood vessels damaged by high blood pressure or other factors. This marker is also a key component in tissues that regulate fluid flow. Working with human eye bank tissue, scientists have detected this molecule in eyes from glaucoma patients but not in eyes from normal controls. This marker is retained when the endothelial cells are grown in the laboratory, thus permitting further molecular characterization of differences between glaucomatous and normal tissue. Two other molecules, NF-kB and interleukin-1, were found only in glaucomatous endothelial cells. The presence of these molecules suggests that the glaucomatous endothelial cells of the trabecular meshwork are reacting to oxidative stress. Scientists speculate that oxidative damage to the trabecular meshwork cells initiates a self-sustaining signaling pathway involving NF-kB, ELAM-1, and inflammatory interleukins. Although this pathway is induced to protect cells, its prolonged activation may initiate glaucomatous damage.

Implications: These results represent a potential break-through in the search for molecular explanations for the pathology of glaucoma. This newly discovered pathway offers fresh insights into the glaucomatous disease state and presents new intervention points for therapy. Scientists can now build on what is known about the role of these molecules in vascular disease. The finding that cells grown in the laboratory retain the characteristics they had *in situ* provides glaucoma researchers with a new tool to further explore the cellular and molecular basis of outflow blockage and test new strategies to prevent disease progression.

Wang N, Chintala SK, Fini ME, and Schuman JS: Activation of a tissue-specific stress response in the aqueous outflow pathway of the eye defines the glaucoma disease phenotype. Nature Medicine 7: 301-309, 2001.

Tomarav SI: Eyeing a new route along an old pathway. Nature Medicine 7: 294-295, 2001.

Spread of Ocular Herpes Simplex Virus Infection in Mice and Humans

Background: Herpes Simplex Virus (HSV) is the leading cause of blindness due to an infectious pathogen in the U.S. After initial infection of mucous membranes in the mouth or the cornea of the eye, the virus invades the nerves and travels to sensory nerve cells that innervate the cornea. Some populations of these nerve cells allow the virus to enter a dormant (latent) state that persists for the life of the infected individual. Reactivation of the latent virus occurs periodically and leads to reappearance and potential spread of virus on the surface of the eye. Repeated cycles of latency and reactivation lead to progressive scarring and clouding of the cornea that, in turn, leads to blindness. Corneal infection is accompanied by periocular disease (spread of virus to the eyelids and conjunctiva) in over 50 percent of the acute infections. This spread causes increased inflammation and exacerbation of symptoms. It is unknown whether these tissues are infected directly during the initial (primary) corneal infection, or are infected by newly formed virus in the nervous system that is subsequently delivered to these tissues via the sensory nerves.

Advance: New molecular genetic techniques were used to monitor and quantify the appearance of viral gene products in an animal model of HSV ocular infection. This permitted tracking the time course of infection in cornea, the nervous system (trigeminal ganglia where the latent virus resides), and the surrounding ocular (periocular) tissues. The studies demonstrated that herpes virus levels peak in the cornea after a day, in the trigeminal ganglia after three days, and in the periocular tissues after the fourth day. This is consistent with spread from the cornea into the nerves and back out to the body surface. Similarly, human spread of virus was documented with a time course that closely mimics that observed in the animal model.

Implications: After HSV infects the cornea, the virus travels to the nerve cells in the trigeminal ganglia and after residing and quickly replicating in the nervous system, to the periocular tissues. This delayed appearance at the surface of the eye suggests that during the acute, primary infection of the cornea, topical antivirals may be insufficient to limit disease, and rapid systemic treatment may be the best means of preventing spread of infection to these tissues.

Summers BC, Margolis TP, and Leib DA: Herpes simplex virus Type 1 corneal infection results in periocular disease by zosteriform spread. Journal of Virology 75: 5069-5075, 2001.

Proyecto Vision Evaluation and Research

Background: The causes and prevalence of blindness and visual impairment are not well documented in the U.S. Mexican-American population. Mexican-Americans are known to have a high rate of diabetes along with more severe hyperglycemia, which indicates poor glucose control. This can lead to major complications of diabetes, including severe diabetic retinopathy and blindness.

Advance: The study *Proyecto VER* (Vision Evaluation and Research) assessed visual impairment in a population-based sample of 4,500 Mexican-Americans age 40 or older, residing in Tucson and Nogales, Arizona. The rate of diabetes in this group was 20 percent, twice the rate reported for non-Hispanic Whites. The rate of diabetic retinopathy in those with diabetes was 48 per cent, a rate similar to that of non-Hispanic Whites. Importantly, 15 percent of study participants did not realize they had diabetes and were newly diagnosed by the study. Among this group of newly diagnosed diabetics, 23 percent had early to moderate diabetic retinopathy, a potentially blinding eye complication of diabetes. Another nine percent had advanced diabetic retinopathy and were in immediate danger of losing some vision. This study points to the need for increased detection of diabetes and regular eye care to provide timely treatment of diabetic eye disease.

Implications: Diabetes increases the risk of blindness 25-fold over the general population. With early detection, timely laser surgery, and appropriate follow-up care, people with advanced diabetic retinopathy can reduce their risk of blindness by 90 percent. This study points to the importance of early diagnosis and treatment of diabetes and the importance of regular, dilated eye exams in this high-risk, minority population.

West SK, Klein R, Rodriguez J, Munoz B, Broman AT, Sanchez R, and Snyder R: Diabetes and diabetic retinopathy in a Mexican-American population. Diabetes Care 24(7): 1204-1209, 2001.

Violent Assaults and Car Crashes Drop in Communities that Have Comprehensive Alcohol-Prevention Program

Background: That intoxication and availability of alcohol are linked to a higher risk of violent assault and car crashes is no surprise. A more difficult conclusion to reach is how to prevent these problems. For the most part, community programs to prevent alcohol-related injuries have focused on fatal car crashes or addressed specific groups; for example, young people. In this 5-year study, investigators sought to change the community environment in a way that would reduce alcohol-related trauma, overall.

The investigators adopted a multi-fold approach to gain community support through coalitions and the media: to help alcohol servers and sellers put in place policies for responsible beverage service, including not selling to minors; enforce underage-sales laws; increase drunk-driving checkpoints and drunk-driving breath-testing; and reduce availability of alcohol outlets through zoning and other municipal tools. Past studies had shown that each of these strategies is useful, but they had not been combined in a comprehensive community approach.

Three ethnically diverse communities took part in the program. Investigators simultaneously monitored three similar communities that did not take part in the program, for comparison. To assess the effectiveness of the intervention, the researchers gathered data on car crashes, surveyed emergency departments, and surveyed 120 people in each of the six communities each month.

Advance: In communities that took part in the program, emergency departments had a 43 percent drop in injuries caused by assault. Car crashes involving drivers who had been drinking dropped by 6 percent, while night-time crashes that involved injuries dropped by 10 percent. Hospitalizations for assault-related injuries dropped by 2 percent. On surveys, self-reports of drinking too much decreased by 49 percent. Self-reports of driving when “over the legal limit” fell by 51 percent.

Implications: Communities are not powerless over their rates of alcohol-related car crashes and violent assaults. They can exert some control by implementing the program described here.

Holder HD, Gruenewald PJ, Ponicki WR, Treno AJ, Grube JW, Saltz RF, Voas RB, Reynolds R, Davis J, Sanchez L, Gaumont G, and Roeper P: Effect of community-based interventions on high-risk drinking and alcohol-related injuries. The Journal of the American Medical Association 284: 2341-2347, 2000.

Policy Changes Reduce Underage Drinking

Background: How to reduce drinking among youth is a complex issue and an urgent one. Drinking among youth holds risk not only for unintentional injury, but also, scientists now suspect, for damage to still-developing nervous systems. Widespread, heavy drinking among adolescents and younger children is of great concern, particularly in view of evidence that initiation of drinking earlier rather than later in youth dramatically increases the risk of becoming alcohol-dependent at some point in life.

Communities Mobilizing for Change on Alcohol (CMCA) was a 6-year trial designed to reduce drinking by young people. Rather than using the traditional approach to preventing underage drinking – that is, focusing on youth’s *demand* for alcohol – CMCA intervened in youths’ *supply* of alcohol. Researchers randomly assigned 15 small-to-midsize Minnesota and Wisconsin communities either to participate in an intervention to reduce drinking by youth or to not participate. Seven of the communities thus organized to change local policies that affected supply of alcohol to youth and made underage drinking less acceptable in the local culture, while the remaining eight communities served as control groups, for comparison.

Advance: Compared to the control communities, CMCA communities had: (1) less drinking by 18-to-20-year-olds, (2) reduced sale of alcohol to minors, (3) reduced provision of alcohol to younger adolescents by older adolescents, and (4) more identification-checking by alcohol merchants, who also were less likely to sell to minors.

Implications: Communities can be mobilized to reduce youths’ access to alcohol. Of particular importance is that the large, controlled trial that produced these results was randomized and that the communities involved had paid little attention to issues surrounding drinking by youth before they were approached by the researchers. Thus, the positive outcomes achieved in the CMCA intervention do not appear to be based on factors that existed in the communities prior to the trial; rather, the outcomes appear to be related to the intervention. These findings suggest that other average communities that commit to the kind of intervention described here could achieve similar results.

Wagenaar AC, Murray DM, Gehan JP, Wolfson M, Forster JL, Toomey TL, Perry CL, and Jones-Webb R: Communities mobilizing for change on alcohol: outcomes from a randomized community trial. Journal of Studies on Alcohol 61: 85-94, 2000.

Early-Onset Drinkers Take More Risks, Sustain More Injuries

Background: Unintentional injury is the leading cause of death for Americans between the ages of 1 and 34. The biggest risk factor for injury is alcohol misuse, and researchers estimate that one-third of deaths from unintentional injury is alcohol-related.

Research has shown that people who begin drinking early in adolescence or childhood are much more likely than others to become alcoholic at some point in life. But does early onset of drinking also portend greater risk of injury throughout life, whether or not a person becomes an alcoholic? Investigators examined data from the National Longitudinal Alcohol Epidemiology Survey, which consisted of a large cross-section of American adults (almost 93,000) in 1992, to find the answers.

Advance: Early onset of drinking is associated with alcohol-related injuries, even when researchers eliminate alcoholism as a factor. Early-onset drinkers were seven times as likely to have put themselves in situations that raised their risk of injury, at some point in life, than were later-onset drinkers.

Implications: At first glance, this finding might seem intuitive. It stands to reason that people who begin drinking earlier in life have a longer drinking span in which to sustain alcohol-related injuries than do people who begin later. But the magnitude of the difference in their injury rate is striking. For example, compared to adults who began drinking after age 21, those who began before age 14 were 12 times as likely to have been injured while drinking or after drinking.

Unintentional injury is a major cause of death and disability. Identifying factors that contribute to it, such as the risk-taking tendency demonstrated by early-onset drinkers, can help us design strategies to prevent it.

Hingson RW, Heeren T, Jamanka A, and Howland J: Age of drinking onset and unintentional injury involvement after drinking. The Journal of the American Medical Association 284: 1527-1533, 2000.

HIV Transmission in Russia

Background: Russia is experiencing one of the sharpest increases in the rate of HIV infection in the world. Forty thousand HIV cases have been diagnosed in Russia, almost all in the last three years, and Russian health authorities expect that one million new cases are likely within two years. To avert a widespread epidemic, improved HIV prevention methods are vital. However, prevention is largely based on behavior change, and little is known about Russian knowledge, attitudes and risk behavior with respect to HIV infection and other sexually transmitted diseases.

Advance: Research supported by NIH has provided essential insights into the behaviors associated with the increased transmission of HIV in St. Petersburg, Russia. In response to a survey, two-thirds of the survey respondents (men and women aged 15-55) acknowledged putting themselves at personal risk of contracting HIV; however, less than 25 percent reported taking any steps to reduce their risk. In a survey of men who have sex with men, four-fifths were bisexual, with approximately one-third reporting female sexual partners in the last three months and nearly 40 percent admitting to unprotected anal intercourse. Although these same men expressed negative attitudes toward the use of condoms, they said they intended to practice safer sex and felt that peer social norms could be changed to support condom use.

Implications: Research reveals similarities between the impending HIV/AIDS epidemic in Russia and existing HIV/AIDS epidemics in other parts of the world. Risky behaviors and sexual practices prevail in the Russian population, related to poor knowledge about AIDS risk, newly openly gay communities, and perceived peer norms that do not support safer sex practices. Russia's economic, cultural, and social upheavals will require both customized and new interventions to bring the burgeoning HIV epidemic under control.

Amirkhanian YA, Kelly JA, and Issayev DD: AIDS knowledge, attitudes and behaviour in Russia: results of a population-based, random-digit telephone survey in St. Petersburg. International Journal of STD and AIDS 12(1): 50-57, 2001.

Amirkhanian YA, Kelly JA, Kukharsky AA, Borodkina OI, Granskaya JV, Dyatlov AA, McKuliffe TL, and Kozlov AP: Predictors of HIV risk behavior among Russian men who have sex with men: an emerging epidemic. AIDS 15: 1-6, 2001.

Kelly JA, Amirkhanian YA, and McAuliffe TL: HIV risk characteristics and prevention needs in a community sample of bisexual men in St. Petersburg, Russia. AIDS Care (in press 2001).

Drug Use and the HIV Epidemic in Northern Vietnam

Background: The spread of HIV related to drug use is increasing dramatically worldwide; in 1999, 114 countries and territories had reported HIV associated with intravenous drug use (IDU), compared to only 52 in 1992. The critical role that drug use and sexual practices of drug users play in spreading the HIV epidemic is now well established, though patterns of drug use differ by country. To effectively design preventive interventions, it is critical to understand the inter-relationship between the two modes of infection, injection drug use and heterosexual contact, within populations. In northern Vietnam, where the opening of the border and changing economic conditions have contributed to increased drug use and commercial sex, there is an urgent need for improved epidemiologic information about the spread of HIV in order to develop more effective prevention and control technologies.

Advance: NIH-supported researchers at the University of California, Los Angeles and counterparts at the National Institute of Hygiene and Epidemiology of Vietnam in Haiphong, a major northern port city, collected information from over 500 drug users between the ages of 15 and 30 to estimate the prevalence of HIV infection among male drug users and to better understand patterns of drug use and sexual behaviors. More than half injected drugs versus snorting or smoking them. HIV prevalence among injection drug users was 25 percent higher than among other drug users. Sharing unsafe equipment was common among this group, and those who shared equipment injected more frequently. Unsafe sex was common among the injecting drug users as well. Nearly one-quarter of the injecting drug users reported receiving an HIV test. Although 81 percent of injecting drug users received pre-test counseling, and 75 percent returned for their results, only 12 percent received post-test counseling, which involved risk reduction advice.

Implications: This study suggests that a range of prevention activities will be critical to reducing the spread of HIV and high risk behavior in drug users in Northern Vietnam. Such activities would include increasing access to condoms, expanding programs to treat drug users, and focussing efforts to provide full services for HIV testing and counseling in a safe environment. Such efforts would be of benefit to drug-using and non-drug-using populations.

Nguyen TA, Hoang LT, Pham VQ, and Detels R: Risk factors for HIV-1 seropositivity in drug users under 30 years old in Haiphong, Vietnam. Addiction 96: 405-413, 2001

Effective Means of Responding to Resurgence of Dengue

Background: The elimination of *Aedes aegypti*, the main vector mosquito of dengue, kept South America relatively free of this viral infection for nearly forty years. The successful campaign, spearheaded by the Pan American Health Organization, was designed to prevent urban yellow fever. In the 1980s, the mosquito re-entered the continent and was followed by another potential vector of dengue, *Aedes albopictus*. Some 2,500 million people – two fifths of the world's population – are now at risk from dengue. The WHO currently estimates there may be 50 million cases of dengue infection worldwide every year. Dengue is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. Although Brazilian health authorities have responded to this reemergence with anti-vector strategies, the relationship between the intensity of *Aedes aegypti* source-reduction efforts and the intensity of dengue transmission has not been evaluated rigorously.

Advance: Researchers from Harvard and the Universidade Federal do Ceará/Brazil correlated a series of dengue outbreaks in Fortaleza, Brazil with data on the density of the vector mosquito. Investigators analyzed data on anti-dengue activities and observed the frequency of dengue cases from information obtained from public records, as well as anti-vector measures, which included the removal of mosquito breeding containers, the treatment of the containers with larvicide, and the spraying of a potent insecticide, malathion. The density of mosquito vectors was expressed as a house index (HI) representing the proportion of inspected houses that contained one or more larval *Aedes aegypti*. Retrospective analysis of anti-vector activity showed that each outbreak was preceded by a relaxed monitoring and source-reduction activity.

Implications: Source-reduction anti-vector interventions are very effective. Since dengue remains suppressed as long as the breeding sites of the vector mosquitoes are reduced, larvicidal source-reduction measures constitute the most efficient mode of preventive intervention.

Pontes RJS, Freeman J, Oliveira-Lima JW, Hodgson JC, and Spielman A: Vector densities that potentiate dengue outbreaks in a Brazilian city. American Journal of Tropical Medicine and Hygiene 62: 378-383, 2000.

Improving Mobility of Nursing Home Residents with Alzheimer's Disease

Background: Three quarters of those with Alzheimer's disease and related dementias are eventually institutionalized. The median nursing home stay for such individuals is 2.75 years, much longer than the national median for all nursing home stays. The nursing home environment frequently encourages physical inactivity, which leads to deconditioning and functional decline. Remobilization and reconditioning is very difficult to accomplish with older adults, and especially with older adults who have dementia. The present study provided structured physical activity in order to slow the rate of physical decline despite probable progression of the underlying dementia. Although several studies among nursing home residents have been conducted with exercise as an intervention, people with Alzheimer's disease and related dementia are excluded from those studies because of difficulties with measurement, treatment compliance and perhaps an assumption regarding the inevitability of the decline. The present study specifically included patients with Alzheimer's disease and excluded those whose cognitive impairment was related to vascular dementia, stroke, Parkinson disease, history of major depression, schizophrenia, or mental retardation. Thirty minutes of self-paced assisted walking, with rest as needed to delay fatigue, was conducted for 16 weeks, three times a week. One group in the study receiving assisted walking also received 30 minutes of conversation about objects and events within their environment.

Advance: The study revealed that conversation alone and assisted walking alone did not significantly slow physical decline over 16 weeks in a population of people with Alzheimer's or related dementias who were long stay residents in a nursing home. However, an exercise program of 30 minutes of assisted walking three times a week including social interaction during walking reduced the rate of decline in physical function among these residents. Maintaining functional independence is a treatment goal for all nursing home residents since it is positively associated with social interaction, maintenance of functional abilities and quality of life.

Implications: Structured assisted walking alone did not significantly slow functional decline in this population. Assisted walking needs to include social interaction in order to improve compliance with the walking intervention. Staff assigned to the seemingly simple task of assisted walking need to use effective communication strategies to gain acceptance of the intervention.

Tappan RM, Roach KE, Applegate EB, and Stowell P: Effect of a combined walking and conversation intervention on functional mobility of nursing home residents with Alzheimer's disease. Alzheimer Disease and Associated Disorders 14: 196-201, 2000.

Psychologic Change in Children with Acute Lymphoblastic Leukemia

Background: Although treatment improvements especially for children have improved dramatically the long term, disease-free survival rates among those with the diagnosis of acute lymphoblastic leukemia (ALL), there are consequences of aggressive treatment. Aggressive treatment includes prophylactic central nervous system therapy with one or more regimen of whole brain radiation, chemotherapy introduced directly into spinal fluid and high-dose chemotherapy. Despite the importance of prophylactic central nervous system treatment, children have been documented to experience declines in intellectual, academic, and neuropsychological skills. The present study examined children with newly diagnosed ALL who were treated with aggressive chemotherapy, in order to determine the pattern of neuropsychologic decline over a four year period.

Advance: The present study demonstrated modest declines in the psychological domains of arithmetic, verbal fluency, and visual-motor skills over four years. The study demonstrates that different factors account for particular cognitive declines. All survivors, regardless of whether they received radiation, systemic chemotherapy or intra-spinal fluid chemotherapy, showed verbal fluency declines, even though other language measures were stable over time. Visual motor skills seem to be particularly vulnerable to disruption by the central nervous system prophylaxis, especially among those children who receive whole brain radiation.

Implications: The present study indicates that outcome and rates of decline, particularly visual-motor skills, vary with respect to differential routes of chemotherapy administration during aggressive central nervous system prophylaxis. Regardless of the underlying mechanism, ALL survivors treated with intra-spinal fluid and intravenous methotrexate may benefit from occupational therapy services, especially those aimed specifically at increasing visual motor coordination and speed. However, occupational therapy is likely not needed for children treated only with intra-spinal fluid chemotherapy. Assuring quality of life for disease-free children with the diagnosis of ALL can be accomplished by specific therapies addressing long term consequences of aggressive chemotherapy.

Espy KA, Moore IM, Kaufmann PM, Kramer JH, Matthay K, and Hutter JJ: Chemotherapeutic CNS prophylaxis and neuropsychologic change in children with acute lymphoblastic leukemia: a prospective study. Journal of Pediatric Psychology 26: 1-9, 2001.

Psychosocial Nursing Therapy after Cardiac Arrest: Impact on Two-Year Survival

Background: Coronary artery disease (CAD) is the leading cause of death and a major cause of disability among men and women in the U.S. About 16 percent of persons hospitalized for acute myocardial infarction have major depression, and by 6 months, 17 percent of those with severe depression have died. The treatment effects of psychosocial therapy on CAD mortality have varied results in the literature. Since it is unknown whether benefits of psychosocial therapy on mortality reduction extend to out-of-hospital sudden cardiac arrest survivors, the present study examined that population.

A sample of 133 survivors of out-of-hospital cardiac arrests were followed for two years. The sample was randomized into two groups, one of which received eleven individual psychosocial therapy sessions given twice a week for about 90 minutes per session. The therapy included a physiologic relaxation training component using biofeedback, a cognitive therapy component aimed at self-management and coping for depression, anxiety and anger, and a health education component focusing on cardiovascular risk factors.

Advance: The present study demonstrated the effectiveness of a nursing psychosocial therapy in the secondary prevention of sudden cardiac death since the treatment group had an 86 percent reduction in risk of cardiovascular death. Specifically, 7 patients had cardiovascular death and 1 death due to stroke in the control group. Only one death due to stroke occurred in the treatment group. The benefits of psychosocial therapy remained strong after controlling for other clinical predictors of death including various pharmacologic therapy.

Implications: Just as in other studies, there is limited explanation for the cause of the improved survival with psychosocial therapy, so further research is needed with various explanatory models. However, despite unclarity about the underlying mechanism, the present study firmly supports the inclusion of psychosocial therapy in the post-cardiac arrest treatment plan for survivors of cardiac arrest.

Cowan MJ, Pike KC, and Budzynski HK: Psychosocial nursing therapy following sudden cardiac arrest: impact on two-year survival. Nursing Research 50: 68-76, 2001.

Targeting Adolescents in Order to Achieve Diabetes Treatment Goals

Background: Diabetes mellitus is the fifth leading cause of death in the U.S., and type 1 diabetes is a major health problem affecting nearly 130,000 U.S. children and adolescents. The findings of the Diabetes Control and Complications Trial (DCCT) found that children over age 13 who achieved better metabolic control from intensive diabetic therapy reduced the risk of complications by 27 to 76 percent. Achieving blood sugar control is the goal of therapy and is usually measured by glycosylated hemoglobin (hemoglobin A1c). However, adolescence is a particularly difficult time to achieve near normal blood glucose values, not only for physiological reasons but also because coping with the physical, emotional, and social demands of self-management of type 1 diabetes can be a formidable task. The difficulty of this task has an impact on adolescents' quality of life.

In the present study, 83 subjects were randomized to two groups: one receiving intensive diabetes management alone and one receiving intensive diabetes management as well as coping skills training (CST). Intensive diabetes management consists of frequent monitoring of blood glucose, frequent insulin injections or insulin pump and frequent alterations of insulin dosage to match diet and activity patterns. The CST occurred in small groups of 2 or 3 subjects with a trainer for six visits, followed by monthly visits.

Advance: Over 12 months, hemoglobin A1c in the treatment group decreased from a baseline of more than 9 percent to a mean of 7.8 percent, and one-third of the subjects achieved the treatment goal of at or less than 7.2 percent. Coping skills training as well as continuing parental support and guidance appear to help adolescents achieve success in metabolic control over one year of follow-up. Quality of life scores were not associated with metabolic control in adolescence.

Implications: The findings suggest that clinicians need to pay as much attention to the youth who is depressed or withdrawn as to the youth whose metabolic control is not in range. Further, for clinicians who intensify treatment with adolescents with poor metabolic control and depression, the result is less likelihood of reaching treatment goals. Last, as past reports have indicated, coping skills training appears to be a powerful method to help teens achieve the metabolic goals of treatment as well as improve their quality of life.

Grey M, Davidson M, Boland EA, and Tamborlane WV: Clinical and psychosocial factors associated with achievement of treatment goals in adolescents with diabetes mellitus. Journal of Adolescent Health 28: 377-385, 2001.

Outcomes of Advanced Practice Nurses in Long-term Care Facilities

Background: The nation's 1.5 million nursing home residents are cared for by a largely unlicensed staff, with physician care provided on a periodic basis every 30 to 90 days or less. Advanced practice nurses (APNs, which are nurse practitioners or gerontological clinical nurse specialists) are being employed in nursing homes, who can work with staff to implement evidence-based protocols for incontinence, pressure ulcers, depression and aggressive behavior. The present study utilized three nursing homes: two employed two APNs for ten hours a week and the third provided usual care.

Advance: From the time of admission to six months, scores revealed significantly greater improvement among residents with APN input in incontinence, pressure ulcers, aggressive behavior, and less deterioration in affect. The mean age of residents across all three sites was 81.6 and most were women. Residents receiving APN treatment over six months demonstrated significantly improved outcomes scores in pressure ulcer, incontinence and aggressive behavior, contrasted to receiving usual care. Among cognitively impaired residents, depression scores improved as well.

Implications: Both the raw numbers of potential residents whose quality of life can be improved by this intervention, as well as the magnitude of averted costs, compel us to examine this intervention. That an intervention can "work" to achieve good outcomes with this population is, itself, a phenomenon that can teach us much about the responsiveness of older adults to treatment. There was a relatively short time (10 hours per week) of intervention, and a concurrently high rate of turnover among unlicensed staff may have weakened the impact of the APNs in the two nursing homes. APNs consistently relied on unlicensed staff to carry out interventions related to prevention or reducing occurrence of urinary incontinence and aggressive behaviors. Once the fiscal outcomes are analyzed, the total study will better inform public policy.

Ryden MB, Snyder M, Gross CR, Savik K, Pearson V, Krichbaum K, and Mueller C: Value-added outcomes: the use of advanced practice nurses in long-term care facilities. The Gerontologist 40: 654-662, 2000.

Postpartum Smoking Behaviors and Immune Response in Mothers of Term and Preterm Infants

Background: Federal data from the Centers for Disease Control and Prevention reported in 1999 that 22.3 million women in the U.S. over the age of 18 smoked cigarettes. There is a relationship between maternal smoking and health problems in infants and young children; 20-30 percent of women in their reproductive years are known to smoke cigarettes. Young children exposed to parents who smoke have an increased number of respiratory infections, an increased prevalence of asthma and impaired development of pulmonary function during childhood. Environmental tobacco exposure is associated with increased occurrence in children of otitis media, tympanotomies, tonsillectomies, cough, bronchitis and pneumonia. Exposure to secondary smoke carries particular risk for infants who are preterm and at low birth weight.

The present study examined 74 mothers of very low birthweight infants and 68 mothers of term infants recruited from two hospitals. Excluded were those mothers who had conditions which might influence immune status: alcohol/drug abuse, infection, anemia or chronic disease. A blood test for a nicotine byproduct, cotinine, was drawn to measure smoking at 1, 2 and 4 months postpartum.

At delivery and at 1, 2 and 4 months, mothers of very low birth weight infants were somewhat more likely to smoke than national estimates for women. Mothers with infants who can least tolerate smoke are more likely to smoke than the general population of childbearing women.

Advance: The present study uncovered patterns of smoking among childbearing women, including mothers of infants with very low birth weight. Women who begin smoking after delivery have no specific pattern of starting to smoke or the amount of cigarettes smoked. Since mothers of very low birthweight infants are likely to have more contact with health care providers, and are more likely to be smoking, there are more opportunities to counsel relating to smoking. There was no impact of smoking on the mothers' immune status.

Implications: This affirms that every encounter with a health care professional should include smoking-cessation advice for women who have a history of smoking, especially women who are mothers of very low birth weight infants.

Gennaro S, Dunphy P, Dowd M, Fehder W, and Douglas SD: Postpartum smoking behaviors and immune response in mothers of term and preterm infants. Research in Nursing and Health 24: 9-17, 2001

Reducing the Risk of Heart Disease in Women with Type 2 Diabetes

Background: Type 2 diabetes affects 90 to 95 percent of the estimated 16 million Americans with diabetes. It is the leading cause of new-onset adult blindness, kidney failure, and non-traumatic lower limb amputations. It also increases the risk of stroke, heart attack, and premature death. Heart disease is two-to-four times more common in adults with diabetes than in their non-diabetic counterparts, accounting for about 50 percent of deaths of people with diabetes. Though deaths from heart disease have fallen dramatically in the U.S., it still remains a major killer of people with diabetes. Women in particular are at a much greater risk of heart disease due to diabetes. Diabetes eliminates the usual female advantage relative to men with respect to death from heart disease.

Advance: A recent study uses data collected over 20 years from The Nurses' Health Study to examine the impact of type 2 diabetes on mortality from coronary heart disease. The Nurses' Health Study cohort consists of over 121,000 female registered nurses between 30 and 55 years of age from 11 U.S. states. Information on diagnosed diabetes and heart disease as well as on other aspects of medical history and lifestyle were collected through questionnaires every two years and validated through medical records obtained on a sample of people in the cohort. Researchers found that type 2 diabetes was associated with dramatically increased mortality from fatal coronary heart disease among women. Compared to women without diabetes, the risk of death from heart disease increased markedly with the duration of diabetes, rising from a 2.75-fold increase in women with diabetes for less than 5 years to a nearly 12-fold increase in women with over 25 years of diabetes. The magnitude of the increased risk of death from heart disease is nearly as great in women with diabetes as in women with a previous heart attack. The combination of a long duration of diabetes and pre-existing coronary heart disease identifies a particularly high-risk group with a 30-fold increased risk of death. The reasons for accelerated atherosclerosis (narrowing of the arteries) in diabetic women are not fully known, however, they are likely related in part to changes in lipid profiles characteristic of women with diabetes.

In addition to documenting the dramatic increase in risk of fatal heart disease, data from the Nurses' Health Study also showed that this risk can be markedly reduced with exercise. Prior research has shown that increased physical activity can reduce the risk for cardiovascular disease in the general population. To determine the role of exercise in reducing risk among individuals with type 2 diabetes, researchers analyzed data from over 5,100 women in The Nurses' Health Study, in whom type 2 diabetes was diagnosed by a physician when they were 30 years of age or older. The diabetic women who spent at least four hours per week performing moderate or vigorous exercise had an approximately 40 percent lower risk for cardiovascular disease than those who did not.

Implications: The findings from the Nurses' Health Study and a similar study of male physicians support the recent change in guidelines for treating lipids in patients with diabetes. Because diabetes confers nearly the same risk of death from heart disease as a previous heart attack, the American Diabetes Association, the National Diabetes Education Program and the National Cholesterol Education Program now recommend aggressive management of cardiovascular risk

factors in diabetic patients, with the same target LDL-cholesterol level for patients with diabetes as for people with a previous heart attack, as well as vigorous control of high blood pressure and lifestyle factors such as smoking, obesity and diet. Exercise plays an important role in the management of type 2 diabetes and is known to be important for control of blood sugar and weight. These new findings suggest it can also decrease the risk for heart disease and stroke in diabetic women. These epidemiological studies provide important insights into prevention of the devastating cardiovascular complications resulting from type 2 diabetes which will be further studied through controlled clinical trials.

Hu FB, Stampfer MJ, Solomon C, Liu S, Colditz GA, Speizer FE, Willett WC, and Manson JE: Physical activity and risk for cardiovascular events in diabetic women. Annals of Internal Medicine 143: 96-105, 2001.

Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, Nathan DM, and Manson JE: The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women. Archives of Internal Medicine 161: 1717-1723, 2001.

Breast Feeding May Limit Teenage Obesity

Background: The prevalence of both overweight and obesity among children, adolescents, and adults has been rising markedly over the past four decades. One of the best-known methods to assess body size is the body mass index, or BMI., a value derived from a person's weight in kilograms divided by his height in meters, squared. Individuals with a BMI of 24-30 are considered overweight, while those with a BMI higher than 30 are classified as obese. Overweight during adolescence predicts short- and long-term morbidity, as well as obesity in adulthood. Because overweight is difficult to treat once the condition exists, it becomes ever more important to prevent it from occurring and potentially progressing to obesity. Obesity in adolescence is a stronger predictor of adult obesity than is obesity in early childhood. Possible consequences of adolescent obesity include cardiovascular risk factors, orthopedic conditions, lower self-esteem, and negative social and economic outcomes in young adulthood. Preliminary epidemiologic data suggests that breastfeeding is associated with a lower risk of subsequent obesity in late childhood and adolescence.

Advance: The objective of a recent study was to assess the extent to which overweight status among adolescents is associated with the type of infant feeding (breast milk vs. infant formula) and duration of breastfeeding. Sons and daughters of participants in the ongoing Nurses' Health Study II comprised the population in the "Growing Up Today Study" that enabled researchers to study these parameters in the context of the prevalence of overweight in older children and adolescents. The main outcome of this study was based on overweight defined as BMI exceeding the age- and sex-specific 95th percentile in a national sample of U.S. children. The results of the study showed that infants who were fed breast milk more than infant formula, or who were breastfed for longer periods, had a lower risk of being overweight during older childhood and adolescence.

Implications: Though nine months was the upper limit for length of breastfeeding in the study, the finding that less overweight correlates with longer duration of breastfeeding supports the recommendation of the American Academy of Pediatrics to continue breastfeeding for the first 12 months of life. These results also suggest that breastfeeding may act as a preventive measure against later overweight, and that its promotion may help to abate the rising prevalence of obesity in the U.S. and in other developed countries.

Gillman MW, Rifas-Shiman SL, Camargo CA Jr, Berkey CS, Frazier AL, Rockett HRH, Field AE, and Colditz GA: Risk of overweight among adolescents who were breastfed as infants. The Journal of the American Medical Association 285: 2461-2467, 2001.

ACE Inhibitor Reduces the Risk of Kidney Failure in African-Americans with Hypertension

Background: African-Americans make up 13.9 percent of the U.S. population, but 29.8 percent of people treated for kidney failure. The increased susceptibility affects all ages, but the racial disparity is most striking in younger age groups; African-Americans between ages 25 to 44 are 20 times more vulnerable to developing hypertensive kidney failure than Caucasians. Better management of high blood pressure has led to fewer strokes and heart disease, but kidney failure is increasing.

Advance: Scientists report that people with kidney disease from high blood pressure have a better chance of reducing the risk of progression to kidney failure if they take an angiotensin-converting enzyme (ACE) inhibitor. A major clinical trial, the African-American Study of Kidney Disease and Hypertension (AASK), found that the ACE inhibitor ramipril (Altace®) slowed kidney disease by 36 percent, and reduced the risk of kidney failure and death by 48 percent, in patients who had at least one gram of protein in their urine (proteinuria). The drug was compared to a dihydropyridine calcium channel blocker amlodipine (Norvasc®). Results were not related to blood pressure control, which was comparable between the study groups. Since 1994, ACE inhibitors have been the preferred treatment for kidney disease associated with diabetes. Based on the results of the current study, the authors recommend the use of ACE inhibitors for patients with kidney disease of hypertension, especially for people who also have proteinuria, which is predictive of eventual kidney failure.

Implications: While calcium channel blockers help many patients, particularly African-Americans, control blood pressure and reduce the risk of stroke and heart disease, patients may need an ACE inhibitor to protect the kidneys. The researchers also recommend measurement of urinary protein excretion to guide initial therapy selection.

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A New Way to Prevent Blood Transfusion Reactions

Background: Blood transfusions offer a lifesaving means for treating traumatic accident victims, surgery patients, and patients suffering from blood disorders such as dialysis-induced anemia, sickle cell anemia, and Cooley's anemia. Patients who require multiple transfusions can develop antibodies against certain molecules frequently found on the surface of transfused red blood cells. Scientists named one such group of molecules the Dombrock blood group after they were detected in blood from a donor named Dombrock in 1965. Antibodies made against Dombrock molecules attack and destroy transfused red blood cells that express them. This immune destruction of transfused red blood cells causes a transfusion reaction, producing fever, chills, lower back pain, vomiting, and blood in the urine. Even though scientists have known about Dombrock molecules for more than 30 years, they have been unable to genotype blood recipients to determine their Dombrock status or to screen for the presence of Dombrock molecules in donated blood until very recently.

Advance: A group of scientists has at last been able to screen differentiating red blood cells and identify the gene coding for the Dombrock blood group molecules. To perform their screen, they used information gleaned from transfused blood undergoing antibody destruction and a linkage study that potentially identified the chromosomal location of the Dombrock molecules. This breakthrough will permit doctors to genotype both recipients and donated blood to determine whether or not they express Dombrock molecules.

Implications: Blood genotyping methods developed with data from this study will help doctors eliminate the painful and frequent bouts of transfusion reaction suffered by patients whose survival depends upon ongoing blood transfusions.

Gubin AN, Njoroge JM, Wojda U, Pack SD, Rios M, Reid ME, and Miller JL: Identification of the dombrock blood group glycoprotein as a polymorphic member of the ADP-ribosyltransferase gene family. Blood 96: 2621-2627, 2000.